ANNALS OF INTERNAL MEDICINE

PUBLISHED MONTHLY BY

The American College of Physicians

VOL. 38 (O.S., Vol. XLIII) MAY, 1953 NUMBER 5

CONTENTS

Page

The Use of ACTH and Cortisone in the Treatment and in the Differential Diagnosis of Malignant Exophthalmos: A Preliminary Report. Laurance W. Kinsell, John W. Partridge and Nadine Foreman 913

The Hyperventilation Syndrome. Bernard I. Lewis 918

Remission of Intractable Allergic Symptoms by Acute Intercurrent Infection. Joseph H. Fries and Stanford Borne 928

Serum Potassium Patterns in Anuria and Oliguria. James Hopper, Jr., Brian P. O'Connell and Hella R. Fluss 935

A Long-Term Evaluation of Aureomycin in the Treatment of Actinomycosis. Leon V. McVay, Jr. and Douglas H. Sprunt 955

Developmental Bronchial Cysts. S. G. Baxter and J. F. Meakins 967

Pure Mitral Insufficiency of Rheumatic Origin in Adults. E. R. Movitt and B. Gerstl 981

Experiences in the Diagnosis and Antibiotic Therapy of Amebiasis: An Analysis of 50 Cases. Nelson J. Weiser, Eugene Spiotta and Pierre Ekman 1002

Testing for Antibiotic Sensitivity in a General Hospital. A. J. Weil and L. Harris 1027

Plasma Cell Myeloma. Gordon C. Meacham 1035

Case Reports:

Large Aneurysm in the Anterior Cranial Fossa: Successful Removal with Recovery. Louis Odessky and David E. Fader 1048

Occurrence of Infectious Mononucleosis and Syphilis in the Same Individual. C. J. D. Zarafonetis 1053

The Use of ACTH in Infectious Mononucleosis. Joseph K. Doran and Austin S. Weisberger 1058

Acute Thyroiditis Treated with Cortisone. S. Lloyd Teitelman and Edward F. Rosenberg 1062

The Treatment of Idiopathic Hemochromatosis by Repeated Phlebotomy. Thomas A. Warthin, Edwin W. Peterson and James H. Barr, Jr. ... 1066

Extraadrenal Pheochromocytomas Exhibiting a False-Negative F 933 Test. Donald F. Gibbs and Neil MacLean 1069

Editorial—Report of Committee on Cardiac Catheterization and Angiocardiography 1081

Reviews 1088

College News Notes 1094

PUBL. APR. 1953 ⟵ A NEW TITLE

IMMUNITY, HYPERSENSITIVITY AND SEROLOGY

By SIDNEY RAFFEL, Se.D., M.D., *Stanford Univ.*

The purpose of this new book is to describe the phenomena of immunity in basic terms, especially with regard to native and acquired resistance to bacteria, viruses and toxins. Logically arranged, it progresses from the theoretical and experimental aspects of immunologic reactions to the important considerations of hypersensitivity, the mechanisms of resistance to infectious diseases and those specific aspects of serology which are of importance in the study of immunity. Practical applications are stressed.

1ST EDITION. APRIL 1953. 531 PAGES. 58 ILLUS. $6.00

PUBL. JUNE 1953 ⟵ A NEW TITLE

PEPTIC ULCER:

PAIN PATTERNS, DIAGNOSIS AND MEDICAL TREATMENT

By LUCIAN A. SMITH, M.D., *Mayo Clinic and Foundation*
ANDREW B. RIVERS, M.D., Late, *Mayo Clinic and Foundation*
with Foreword by GEORGE B. EUSTERMAN, M.D.

This book presents the latest tested methods for the precise diagnosis and satisfactory medical management and treatment of the peptic ulcer. It is unique in its emphasis on careful clinical evaluation of specific diagnostic pain patterns, methods for the prevention of recurrence, and an educational form of therapy which leads to full cooperation by the patient in resuming daily activities with frequently lasting comfort. The illustrative material is most valuable.

1ST EDITION. JUNE 1953. 575 PAGES. 218 ILLUS. $13.50

PUBL. JUNE 1953 ⟵ NEW 12TH EDITION

HOLT PEDIATRICS

(Formerly Holt's Diseases of Infancy and Childhood)

By L. EMMETT HOLT, JR., M.D., F.A.A.P.
and RUSTIN McINTOSH, M.D., F.A.A.P.
with MORE THAN 60 COLLABORATING AUTHORITIES

For 50 years succeeding editions of "Holt" have expressed practical pediatrics in terms of the fundamental precepts of clinical science. This rewritten edition, the 1st since 1940, maintains that tradition and is clearly written, thorough in its coverage and entirely up to date in its detailed methods of prevention, diagnosis and treatment.

The authors and their collaborators have a background of broad experience in all phases of pediatric research, clinical teaching and successful practice. The result is an intelligent blending of the theoretical and practical considerations affecting the physical, mental and emotional development of children, and the recognition and effective treatment of the diseases and injuries to which they are subject.

12TH EDITION. JUNE 1953. 1542 PAGES. 362 ILLUSTRATIONS. $15.00

APPLETON-CENTURY-CROFTS, INC.

35 WEST 32ND STREET, N.Y. 1, N.Y.

Subscription per annum, net postpaid, $10.00, United States, Canada, Mexico, Cuba, Canal Zone, Hawaii, Puerto Rico, Philippine Islands, Central and South American Countries, and Spain; $11.00, other countries.
Entered as Second Class Matter August 21, 1928, at the Post Office at Lancaster, Pa., under the Act of March 3, 1879. Acceptance for mailing at a special rate of postage provided for in the Act of February 28, 1925, embodied in paragraph (d-2), section 34.40, P. L. & R. of 1948, authorized October 7, 1950.

HOW COMPLETE IS YOUR HEART LIBRARY?

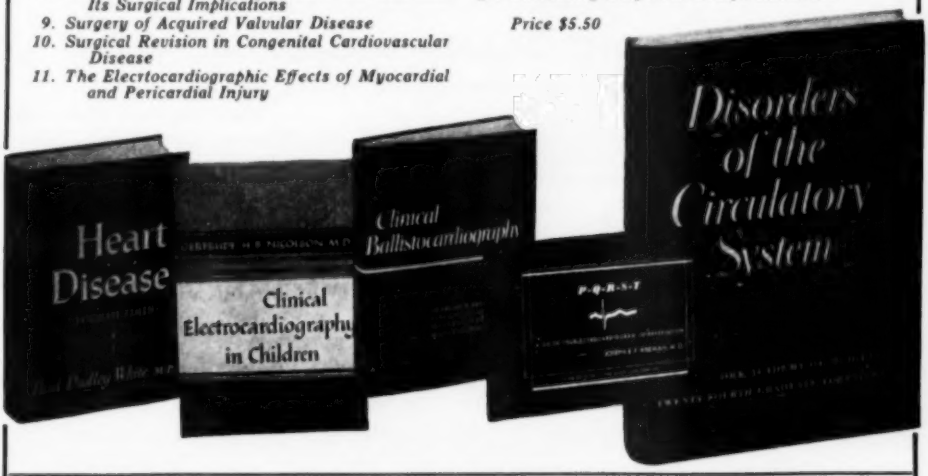
Five new books on the cardiovascular system:

DISORDERS OF THE CIRCULATORY SYSTEM. *A Symposium edited by Robert L. Craig, M.D., under the auspices of The New York Academy of Medicine's Graduate Fortnight Series*

Contents

1. *The Role of the Connective Tissue in Diseases of the Cardiovascular System*
2. *Contraction in the Heart Muscle Fiber*
3. *Lipid Metabolism and Atherosclerosis*
4. *Diet and Lipotropic Agents in Atherosclerosis*
5. *Coronary Disease: Clinical-Pathologic Correlations and Physiology*
6. *The Clinical Recognition of Coronary Heart Disease*
7. *The Importance of Cardiac Arrhythmias*
8. *Pathologic Physiology of Mitral Stenosis and Its Surgical Implications*
9. *Surgery of Acquired Valvular Disease*
10. *Surgical Revision in Congenital Cardiovascular Disease*
11. *The Electrocardiographic Effects of Myocardial and Pericardial Injury*
12. *Edema and Dyspnea of Heat Failure*
13. *The Mechanism and Management of Circulatory Failure*
14. *The Treatment of Some Bacterial Infections of the Heart and Pericardium*
15. *Humoral and Vasomotor Controls of Blood Vessels*
16. *Endocrine Factors in Hypertension*
17. *The Medical Therapy of Acute and Chronic Arterial Occlusion*
18. *The Surgical Therapy of Acute and Chronic Arterial Occlusion*
19. *Circulatory Responses in Life Situations*

Price $5.50



HEART DISEASE, *4th edition*
by Paul Dudley White, M.D.

This new edition of the classic on heart disease will bring you entirely up to date on the etiology, pathogenesis, diagnosis, and treatment of this illness. The chapters on electrocardiography have been rewritten, and the interesting techniques of electrofluorokymography and ballistocardiography are included. Much attention has been given to current research in the preventive aspects of heart disease. *Price $12.00*

CLINICAL ELECTROCARDIOGRAPHY IN CHILDREN
by Gertrude H. B. Nicolson, M.D.

Here is a study written for the general practitioner, the pediatrician, and the cardiologist, delving into the various aspects of the normal and abnormal child's heart. To further assist the profession's understanding of this subject, Dr. Nicolson has used the tracings of 350 young normal adults for comparison with the children. *Price $3.25*

CLINICAL BALLISTOCARDIOGRAPHY
by Drs. Brown, DeLalla, Epstein, and Hoffman

A brand new science has progressed from the research stage to important office procedure. This book will tell you when to use ballistocardiograph instruments, and how to interpret your findings. *Price $5.50*

P-Q-R-S-T, *3rd edition*
by J. E. F. Riseman, M.D.

Save your time, Doctor, with this handy guide to electrocardiogram, interpretation. New in approach, P-Q-R-S-T is designed in handy pocket size and it shows in pictorial form how to proceed step-by-step in the analysis of an electrocardiogram, and contains all the known aspects of the newer V and aV leads. *Price $4.00*

The Macmillan Company

60 FIFTH AVENUE, NEW YORK 11, N. Y.

READY NOW

2nd Edition, 1953—New—Complete—Up to Date

PSYCHIATRIC DICTIONARY

With Encyclopedic Treatment of Modern Terms

By Leland E. Hinsie, M.D., Clinical Professor of Psychiatry, College of Physicians and Surgeons, Columbia University, and Jacob Shatzky, Ph.D., Research Librarian, New York State Psychiatric Institute and Hospital.

Second Edition, 1953. 804 Pages. 2 Volumes in 1. Cloth, $15.00.

Since the publication of the *Dictionary* in 1940 hundreds of new terms and concepts have been added to psychiatric literature. In this separate supplement incorporated with the original text over 900 new words are defined in the form of clinical observations. The same procedures in spelling, pronunciation, and derivation of terms have been followed and the use of over 2,343 cross-references make this supplement a unified, integral part of the original work. Since many of the added words are new, it has been found necessary to treat them at greater length. The new material added increases by approximately one third the total contents of the work. The supplement consisting of over 900 new title entries, all in current usage, brings the *Dictionary* completely up to date.

PSYCHIATRIC DICTIONARY—Supplement Only—Part II

By Leland E. Hinsie, M.D., Jacob Shatzky, Ph.D., Judah A. Joffe, Executive Editor.

1953. 228 Pages. Bound separately, Cloth, $7.00.

For the benefit of those who may have purchased the original edition of the *Dictionary*, this Supplement of over 900 title entries is made available in separate form. Since the printing of the individual Supplement is limited, it is suggested that orders be placed promptly if it is desired to complete the *Dictionary* in two volumes.

OXFORD UNIVERSITY PRESS, INC., 114 Fifth Ave., New York 11, N.Y.

WHY USE OUT-MODED APPARATUS FOR MECHANICAL DRAINAGE OF

MASSIVE EDEMA

WHEN IT CAN BE ACCOMPLISHED TWICE AS EFFECTIVELY BY THE USE OF

SOUTHEY-LEECH TUBES*

DON'T WAIT UNTIL THE NEED IS IMPERATIVE.

HAVE THEM ON HAND

*Flesa, M. J., and Thayer, J. M.: Archives, Int. Med. 85:132 (Jan. 1950

—— *Prepare for that emergency—Clip Coupon Now* ——

Please send ____ sets of Southey-Leech Tubes, complete with trocar and drainage tubing at $12.00 per set to:

Name: _____

Street: _____

City: _____

Tubes and trocar made of rust-resistant, silver-nickel. Will last indefinitely. Order a set to have on hand. Ask your hospital to keep them on hand.

The Briggs Company

82 WATERMAN ST.

PROVIDENCE 6, RHODE ISLAND

Now . . . NEW 2nd Edition!

THERAPEUTICS in Internal Medicine

★ WHAT
★ WHEN
★ HOW
of
INTERNAL MEDICINE

By 84 Authorities

Edited by

FRANKLIN A. KYSER, M.D., F.A.C.P.

Assistant Prof. of Medicine
Northwestern Univ. Medical Sch., Chicago

Attending Physician, Evanston Hospital, Evanston, Ill.

Second Edition, Completely Revised and Reset

827 pages

For the general practitioner or the specialist doing internal medicine, Kyser's THERAPEUTICS will prove a boon in daily practice. The busier you are the more helpful it can be. Each of 300 conditions is discussed by one authority who describes the best treatment known today and explains specifically *What* to do, *When* to do it—and *How* to carry out the recommended procedures. There is no conflicting advice. For every treatment question you will find a reliable answer.

By confining the book to internal medicine all useful detail can be included in one convenient volume. Nothing useful is omitted to save space.

To appreciate fully how valuable this book can be you will want to try it in your own office *before* you buy it. Simply send for it on approval—examine it carefully—keep it on your desk for a while—then decide. But be sure to return the convenient coupon now!

PAUL B. HOEBER, Inc.
Medical Book Department of Harper & Brothers
49 E. 33rd Street, New York 16, N. Y.

Please send me On Approval for free examination before I buy it.

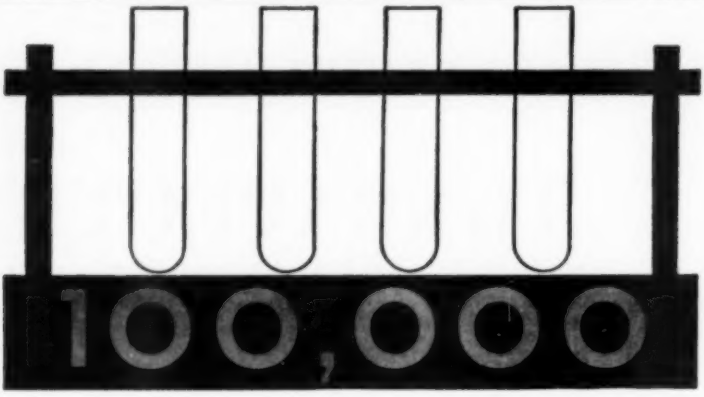
Kyser's THERAPEUTICS IN INTERNAL MEDICINE.....$14.00

☐ Bill Me ☐ Check Enclosed . . (full return privileges, of course)

Name.....

Address.....

City.....Zone.....State.....



over

diabetes detection centers!

"The ideal detection center is the office of the family physician."[1]

Increasing experience in diabetes case-finding indicates that intermittent surveys and mass screening drives, although useful, have certain limitations. Getting and others,[2] in evaluating a community detection campaign (well publicized in the area), report that only 59% of persons accepting the free testing materials actually performed the test. Only 24% of those with positive results sought medical advice.

To find the estimated one million unknown diabetics[3] and place them under needed medical care, the indispensable factor for success is the activity of the individual physician.

1. Blotner, H., and Marble, A.: New England J. Med. *245*:567 (Oct. 11) 1951.
2. Getting, V. A., and others: Diabetes *1*:194, 1952.
3. Wilkerson, H. L. C., and Krall, L. P.: J.A.M.A. *135*:209 (Sept. 27) 1947.

DIABETES DETECTION IN DAILY PRACTICE — a nationwide poll

To assist in the compilation of nationwide data on diabetes, gained through the experiences of private practitioners, Ames Company recently mailed a questionnaire to the medical profession. Your reply will become a vital part of a statistical study to be published on the results of this questionnaire.

AMES COMPANY, INC. **Elkhart, Indiana** Ames Company of Canada, Ltd., Toronto

makers of CLINITEST® Reagent Tablets for detection of urine-sugar

Variety Is the Key to Palatable 'Carbo-Resin' Therapy

New 'Carbo-Resin,' Unflavored, can be subtly hidden in the texture and flavor of many tasty items, such as fruit juices, cookies, and numerous desserts.

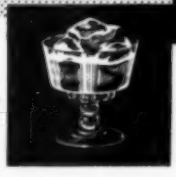
Patients will welcome this satisfying variety in their daily 'Carbo-Resin' doses. Directions for preparing many enticing foods containing the unflavored powder appear in a recipe booklet now being distributed to physicians.

'Carbo-Resin' is indicated in heart disease, cirrhosis of the liver, edema of pregnancy, and hypertension or whenever low-sodium diets are indicated. Complete literature is available upon request.

Eli Lilly and Company
Indianapolis 6, Indiana, U. S. A.

Suspended in orange juice

Baked into brownies or cookies



Blended into gelatin dessert

Lilly

Supplied in two forms—flavored and unflavored. Only 'Carbo-Resin,' Unflavored, is suitable for incorporation into recipes.

POWDER

'Carbo-Resin'

(CARBACRYLAMINE RESINS, LILLY)

Ann Woodward
Director

DO YOU WANT TO MEET THIS MAN?

A MAN WALKED INTO OUR OFFICE YESTERDAY—A PHYSICIAN WHOSE EXCEPTIONAL QUALIFICATIONS will certainly win early recognition for him in some fine hospital or with some farsighted group of practitioners.

Training. Experience. Age. Working capacity. Personal adaptability. On all these counts, this outstanding candidate's rating is high, and somewhere his abilities are going to be promptly and decisively welcomed.

Possibly he is the man *your* hospital or *your* office has sorely needed. If this should be the case, we do indeed covet the satisfaction of presenting his credentials! . . .

Have we a list of your current personnel needs, medical and ancillary?

OUR 57th YEAR
WOODWARD . .
Medical Personnel Bureau
FORMERLY AINGE'S
• 3rd FLOOR • 185 N. WABASH • CHICAGO 1 •

YOUR ATTENTION

To the advertising pages of this journal is recommended by the Advertising Committee. This committee controls the acceptance of promotional material in the **Annals of Internal Medicine** in the interest of its readers. The committee accepts advertisements only of worthy products or competent services offered by reputable firms. It refuses all that is irrelevant to the practice of internal medicine.

The **Annals** reader who examines the informative and attractive advertisements in each issue takes one more step in keeping abreast of newer developments in clinical medicine.

Obocell®

DOUBLE THE POWER TO RESIST FOOD

IN OBESITY

Each OBOCELL tablet contains:
Dextro-Amphetamine Phosphate . . 5 mg.
*Nicel . . . . . 150 mg.

Suppresses bulk or hollow hunger, curbs the appetite and elevates the mood.

Supplied: Bottles of 100, 500, 1000.

*Irwin Neisler's Brand of High Viscosity Methylcellulose

IRWIN, NEISLER & COMPANY
DECATUR, ILLINOIS

To reduce blood pressure and alleviate hypertensive symptoms

In discussing antihypertensive therapy, Grimson and co-workers conclude ". . . hexamethonium seems to be the best present medical approach toward blockade of the sympathetic nervous system."[1]

With Methium (hexamethonium chloride), *orally effective* ganglion blocking makes it possible to:

1. reduce blood pressure to normal or near-normal levels
2. produce marked subjective improvement. Even when blood pressure is not lowered significantly, headaches, dizziness, palpitation and other complaints disappear in the majority of cases.

Also, "Papilledema and retinal damage usually regress. Cerebral edema and vomiting can be relieved. Pulmonary edema may be lessened or resolved and cardiac hypertrophy diminished."[2]

Methium is particularly indicated in severe hypertension. In malignant hypertension it is known to stay the rapid progress of the disease. Induction of lower blood pressure and increase of dosage should be gradual. Once maximal therapeutic benefit is obtained, dosage can be stabilized and therapy maintained indefinitely.

Methium is a potent drug and should be used with particular caution when complications exist —impaired renal function, coronary artery disease and existing or threatened cerebral vascular accidents. Complete instructions for the use of Methium are available and should be consulted prior to instituting Methium therapy.

Methium is supplied in both 125 mg. and 250 mg. scored tablets in bottles of 100 and 500.

1. Grimson, K. S.; Orgain, E. S.; Rowe, C. R., and Sieber, H. A.: J.A.M.A. 149:213 (May 17) 1952.
2. Paton, W. D. M., and Zaimis, E. J.: Pharm. Reviews 4:219 (Sept.) 1952.

Methium® CHLORIDE

BRAND OF HEXAMETHONIUM CHLORIDE

WARNER-CHILCOTT *Laboratories* NEW YORK

PIONEERING THE FIRST

TRUE HEMATOPOIETIC STIMULANT

IN ANEMIA THERAPY

Specific Bone Marrow Stimulation

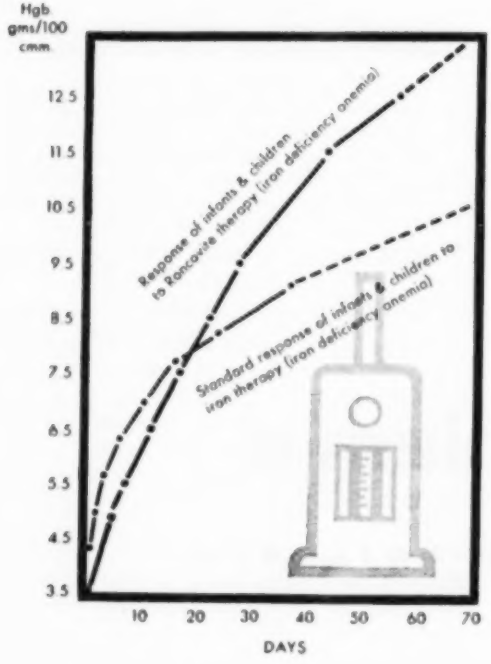
An entirely new approach to the successful treatment of human secondary anemia has been opened up with the introduction of the first true hematopoietic stimulant—Roncovite.

Roncovite offers, for the first time, the specific bone marrow erythropoietic action of cobalt—with adequate iron for the formation of hemoglobin.

In iron deficiency anemia where iron has been the standard treatment, Roncovite produces a faster response, greatly superior erythropoiesis and up to fourfold increases in the utilization of iron. [1, 2]

In the anemia accompanying infection or chronic inflammatory disease, where iron is useless, Roncovite provides—in many cases—a striking and dramatic hematopoietic response. [3, 4, 5, 6, 7]

The above clinical findings mean that Roncovite offers a significant advance in the treatment of all types of "secondary" anemia.



Comparison of the response of hypochromic anemic infants and children to Roncovite and to iron; with Roncovite, iron utilization was so efficient that 58% of the ingested iron was converted to hemoglobin[2]—as compared to the usual average of 15% utilization from ferrous sulfate.—

Standard response chart, Josephs, H.: J. Pediat. 49:246 (1931).

RONCOVITE*

RONCOVITE—PIONEERED BY LLOYD RESEARCH

Tablets—each enteric coated, red tablet contains:

Cobalt chloride (Cobalt as Co...3.7 mg.).....15 mg.
Ferrous sulfate, exsiccated (Iron as Fe...60 mg.) .....0.2 Gm.
Average adult dosage—1 tablet after each meal and at bedtime.

Supplied in bottles of 100 tablets.

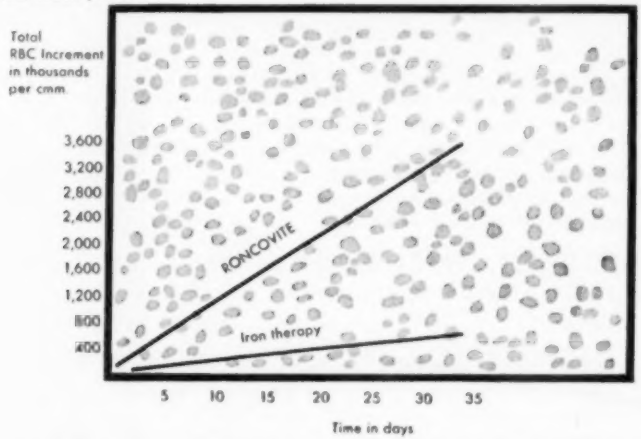
Drops—each 0.6 cc. contains:

Cobalt chloride (Cobalt...9.9 mg.).....40 mg.
Ferrous sulfate (Iron...15.1 mg.).....75 mg.
Average dose—0.6 cc. (10 minims) diluted with water, milk, fruit or vegetable juice once daily to infants and children.

Supplied in bottles of 15 cc. with calibrated dropper.

1. Wolff, H.; Med. Monatsschr. 5:239 (1951); (2) Rohn, R.J., and Bond, W.H.: to be published; (3) Berk, W., et al: New England J.M. 240:754 (May) 1949; (4) Robinson, J.C., et al: New England J.M. 240:749 (May) 1949; (5) Weissbecker, W., and Maurer, R.: Klin. Woch. 24:855 (1947; (6) Wolff, H., and Barthell, S.: Munch. M. Wschr. 93:467 (1951); (7) Gardner, F.H.: J. Lab. & Clin. M. 41:56 (Jan.) 1953.

*The pioneer cobalt product.



Comparison of the average erythrocyte response of iron-deficiency anemic children to Roncovite[2] and to iron therapy.—Computation—Method of Schiodt: Am. J. Med. Sci. 193:313 (1937).

LLOYD BROTHERS, Inc., Cincinnati 3, Ohio
In the Interest of Medicine Since 1870

TASTI-DIET

low-calorie

DIETETIC FOODS

boon to the millions whose caloric intake must be reduced

Theoretically it is not difficult to organize a diet which will adequately reduce the caloric intake of the individual so that orderly weight loss occurs. If human beings ate only to satisfy hunger, it would not be so difficult for obese patients to stay on a weight reduction regimen.

Their excessive appetites and the exaggerated importance which eating occupies in their lives may well be related to psychologic aberrations and obscure frustrations. It is this very perversion of the appetite that makes it so difficult for the obese to remain on the reducing diet—so many of the foods prohibited are the very ones that are most pleasurable.

Even on a well-organized high-protein diet, in which hunger is held in complete abeyance, the craving for something sweet becomes more and more intense, and if self-discipline is not sufficiently rigid, "cheating" results.

Tasti-Diet Low-Calorie Dietetic Foods are especially designed to overcome this problem. Because of their unique processing (without sugar) their caloric content is as much as 70% less.

Tasti-Diet Dietetic Foods—an array of 36 low-calorie fruits, vegetables, salad dressings, puddings, jellies, and gelatin desserts—can make the difference between success and failure in any weight reduction program. Through their use the reducing diet can provide—within the realm of the proper caloric limitation—an abundance of salads with tasty dressings, luscious fruits in a sweet, rich, syrup-like liquid, delicious desserts and jellies that satisfy the craving for sweets.

Physicians are invited to send for literature and a representative sample of each category of the foods mentioned.

FLOTILL PRODUCTS, INCORPORATED

TASTI-DIET DIETETIC FOODS DIVISION

Stockton, California

TASTY JELLIES

Tasti-Diet Dietetic Foods are special purpose foods processed to meet specific dietetic needs. Tasti-Diet canned fruits, jellies, and desserts (no sugar added) are sweetened with nonnutritive artificial sweeteners; Tasti-Diet canned vegetables are processed without the addition of salt or sugar; Tasti-Diet dressings, containing no sugar or mineral oil, are prepared especially for low-calorie, low-sugar, and diabetic diets.

LUSCIOUS CHERRIES

DELECTABLE SWEET FIGS

RICH RIPE PEACHES

DELICIOUS CUSTARDS

GELATIN DESSERTS

TANGY DRESSINGS

to establish "HABIT TIME"...
to control constipation...

Petrogalar—for constipation and as an adjunct to a rational regimen of diet and exercise.

PETROGALAR®

Aqueous Suspension of Mineral Oil

Wyeth®
Philadelphia 2, Pa.

announcing

"THIOSULFIL"®

BRAND OF SULFAMETHYLTHIADIAZOLE

the more soluble sulfonamide for greater safety in treating urinary tract infections

Check these features and advantages

	RAPID BACTERIOSTATIC ACTION
HIGHER SOLUBILITY	LOW DOSAGE LEVELS
LOWER ACETYLATION	MINIMUM TOXICITY
PROMPT ABSORPTION	LESS RISK OF SENSITIZATION
RAPID EXCRETION	NO ALKALINIZATION
	NO FORCING OF FLUIDS

Supplied: No. 785—0.25 Gm. per tablet (scored)—bottles of 100 and 1,000.

Suggested Dosage:

ADULTS

Mild infections—1 tablet (0.25 Gm.) five to six times daily. Severe infections, mixed infections, or where bacterial resistance is expected—2 tablets (0.5 Gm.) five to six times daily.

INFANTS AND CHILDREN

½ to 1 tablet (0.125 to 0.25 Gm.) five to six times daily.

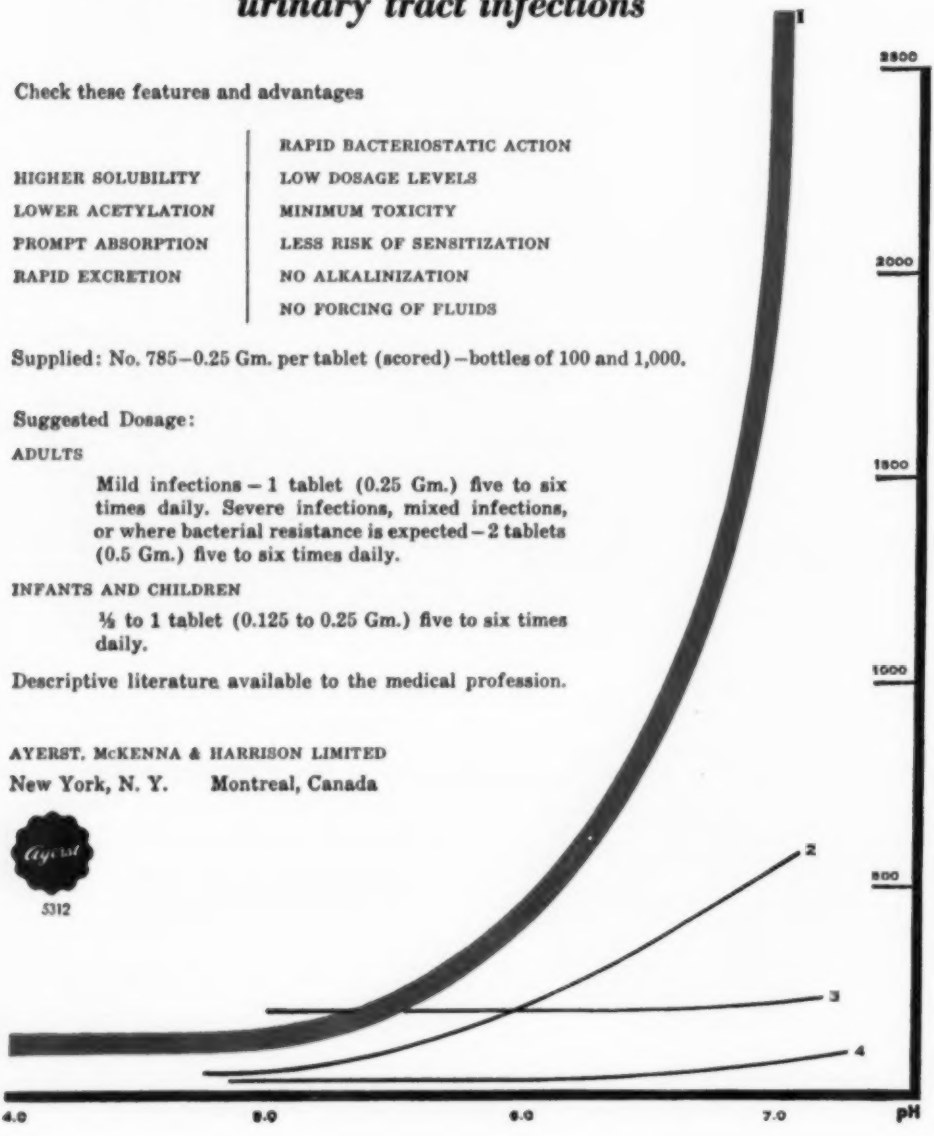
Descriptive literature available to the medical profession.

AYERST, McKENNA & HARRISON LIMITED

New York, N. Y. Montreal, Canada

Ayerst

5312

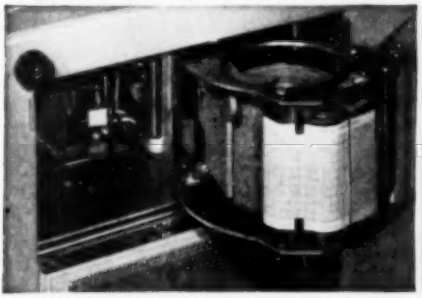


NEW GE Cardioscribe offers 5 big advantages

Here's General Electric's answer to your demands for faster, easier, more accurate electrocardiography. It's the *all-new* GE Cardioscribe. Take a look at the five outstanding features shown here. But they're only part of the story! For full information, see your GE x-ray representative, or write X-Ray Department, General Electric Company, Milwaukee 1, Wisconsin, for Pub. M-5.

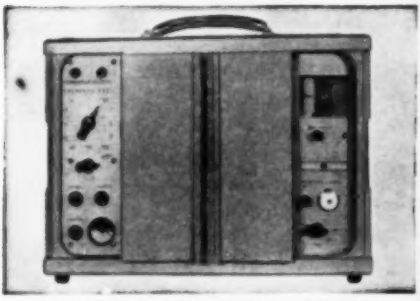
GENERAL ELECTRIC

1 **Self-stabilized** — No more undiagnosible tracings due to line-voltage fluctuations, and stabilization time between leads has been cut.



2 **Improved paper drive** — Operates independent of stylus, is easily loaded, can be quickly adjusted for correct paper tension.

3 **Exclusive chest selector switch** — You can connect individual chest electrodes and check six positions — all in just 10 minutes!



4 **New design** puts controls at your finger-tips. Dual, recessed, hinged tops cover controls — support no weight when unit is carried.

5 **30-lead selection** — Once all electrodes are positioned on the patient you can get 30 leads by simply rotating the selector switches.

For Prevention of Angina Pectoris

Tolerance and toxicity, twin dangers of the older nitrates and nitrites, are not associated with METAMINE, the unique, new cardiac trinitrate with a nitrogen instead of the usual carbon linkage. Four METAMINE tablets daily, after meals and at bedtime, usually eliminate anginal attacks altogether or greatly reduce their number and severity. Supplied in vials of 50 tablets.

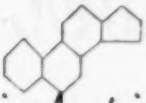
Metamine®

TRIETHANOLAMINE TRINITRATE BIPHOSPHATE TABLETS, 2 MG.

Write for literature and a clinical trial supply.

Thos. Leeming & Co. Inc. 155 EAST 44TH STREET, NEW YORK 17, N. Y.

cortisone + SCHERING = Cortogen

the symbol SCHERING denotes leadership in steroid hormone  research and manufacture -- including Cortogen in the most useful clinical forms. For systemic therapy, use Cortogen tablets SCHERING or injection . For eye disorders use Cortogen ophthalmic suspension -- sterile . The Schering seal SCHERING appears on each tablet and package -- your assurance of quality.

CORTOGEN®

Acetate (cortisone acetate, Schering) Tablets, 5 mg. and 25 mg.;
Injection, 25 mg. per cc., 10 cc. multiple-dose vials;
Ophthalmic Suspension—*Sterile*, 0.5% and 2.5%, 5 cc. dropper bottles.

Schering CORPORATION · BLOOMFIELD, NEW JERSEY
In Canada: Schering Corporation, Ltd., Montreal

CORTOGEN

SCHERING

"of the newer antibiotics

Fumidil

TRADE MARK

(Fumagillin, Abbott)

appears to be the most promising as a direct-acting amebicide"[1]

FUMIDIL is direct acting

FUMIDIL, unlike the broad spectrum antibiotics, is directly amebicidal. It has no antibacterial spectrum, and does not affect normal flora in the intestinal tract.

FUMIDIL is well tolerated

At the recommended dose, side effects from FUMIDIL have been transient and have rarely been of such significance as to justify the interruption of therapy.

FUMIDIL is specific for amebiasis

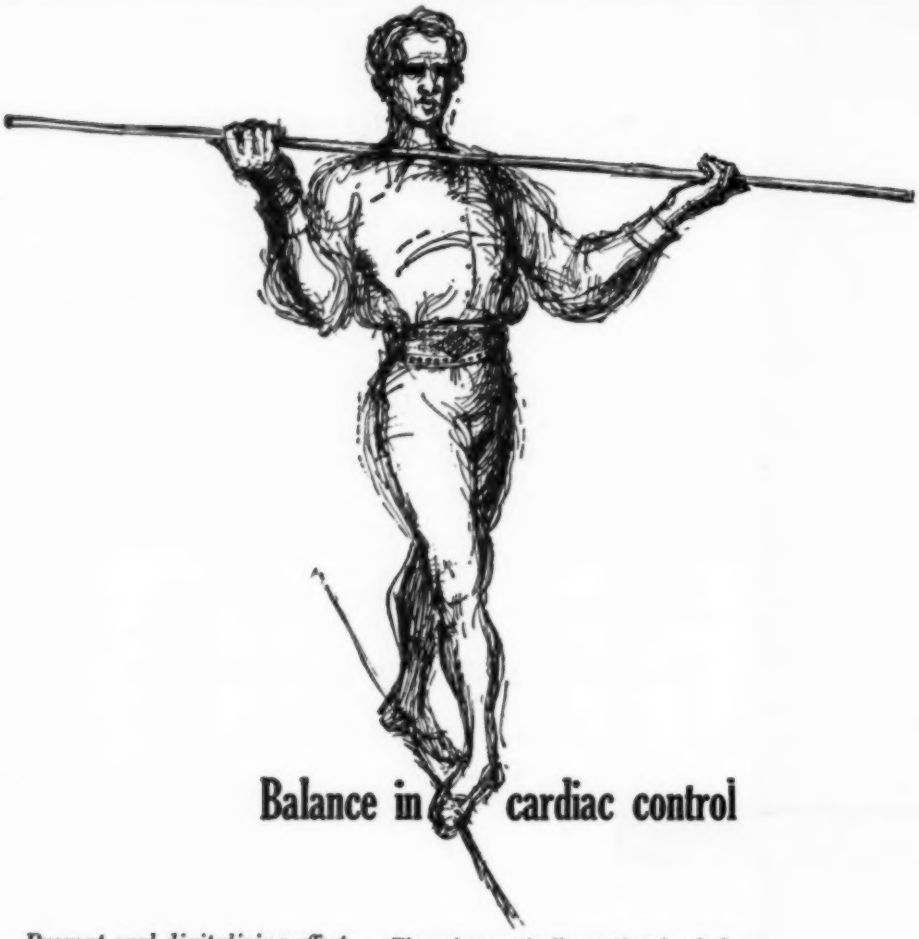
FUMIDIL acts specifically against *E. histolytica*—both in the trophozoite and cyst forms. Danger of overgrowth of yeasts and fungi is slight, and all reported studies show low incidence of recurrence.

FUMIDIL is effective orally

Recommended dosage for the average adult is 30 to 60 mg. daily, in divided doses three or four times a day, for 10 to 14 days. One course usually clears most cases. In 10-mg. capsules, bottles of 30. Abbott

1. Anderson, H. H., et al. (1952), Fumagillin in Amebiasis, Amer. J. Trop. Med. & Hyg., 1:552, July.

1-162



Balance in cardiac control

Prompt oral digitalizing effect . . . There is practically no time lag before the action of orally administered Digoxin; it is apparent within an hour. Relief of symptoms of cardiac failure is complete in about six hours, and full digitalization is achieved in eighteen to twenty-four hours.

Even maintenance . . . The rate of elimination of Digoxin is unique; it is fast enough to permit rapid control of toxicity in case of overdosage[1]; it is not so rapid as to give fleeting peaks of effect. This balance provides both a practical margin of safety and steady maintenance.

Digoxin / **'B.W.&Co.'®**

Preparations available:

- 'Tabloid'® brand Digoxin 0.25 mg. for oral digitalization and maintenance.
- 'Wellcome'® brand Digoxin Injection 0.5 mg. in 1 cc. for rapid digitalization by intravenous injection (after dilution with 10 times its volume of saline).

1. Schaaf, R. S., Hurst, J. W., and Williams C.: Med. Clin. North America (Mass. Gen. Hosp. No.) p. 1255 (Sept.) 1943.

Burroughs Wellcome & Co. (U.S.A.) Inc., *Tuckahoe 7, N. Y.*

speaking of allergy, let's get down to cases

The documented record – more than 900 reports – shows literally thousands of allergic patients relieved of symptoms by Pyribenzamine. Relief has been prompt and prolonged, with extremely low incidence of sedation or other side reactions.

On the basis of published evidence, no other antihistamine combines greater clinical benefit with greater freedom from side effects. *Supplied:* Pyribenzamine hydrochloride (tripelennamine hydrochloride Ciba) 50 mg. (scored) tablets, bottles of 100 and 1000.

Pyribenzamine®

For A.M.A. Conventioners

GUIDE TO NEW YORK CITY

As a special service to Doctors who will attend the forthcoming A.M.A. Convention, Ciba has prepared a comprehensive *Guide to New York City* which describes points of interest, restaurants, entertainment, etc.

For your complimentary copy, write to Dept. 510, Ciba Pharmaceutical Products, Inc., Summit, N.J.

z/10110

Ciba

For every age group...

this
Broad Spectrum
DIETARY SUPPLEMENT

Regardless of cause or patient age, the need for dietary supplementation frequently arises. Whenever such supplementation is indicated to round out the intake of essential nutrients, a truly broad spectrum supplement—one that supplies notable amounts of all important nutrients—will serve the patient optimally.

Ovaltine in milk, a delicious food drink, has long been widely prescribed for this purpose. As the appended table shows, it supplies substantial amounts of virtually all nutrients known to take part in metabolism, from biologically top-grade proteins, through the gamut of the essential vitamins, to the minerals needed in trace amounts.

Whenever the patient's nutritional state must be improved, Ovaltine deserves the physician's first consideration.

THE WANDER COMPANY, 360 N. MICHIGAN AVE., CHICAGO 1, ILL.

Ovaltine

Three Servings of Ovaltine in Milk Recommended for Daily Use Provide the Following Amounts of Nutrients

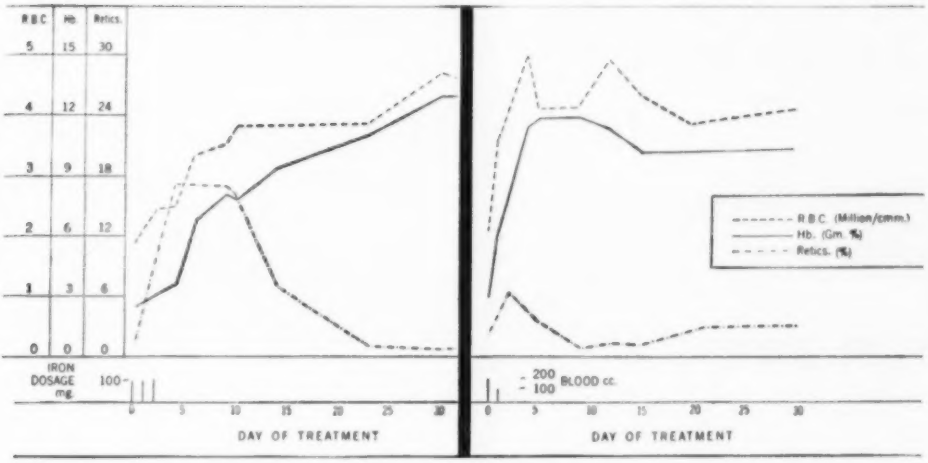
(Each serving made of ½ oz. of Ovaltine and 8 fl. oz. of whole milk)

MINERALS		VITAMINS	
*CALCIUM	1.12 Gm.	*ASCORBIC ACID	37 mg.
CHLORINE	900 mg.	BIOTIN	0.03 mg.
COBALT	0.006 mg.	CHOLINE	[illegible] mg.
*COPPER	0.7 mg.	FOLIC ACID	0.05 mg.
FLUORINE	3.0 mg.	*NIACIN	6.7 mg.
*IODINE	0.15 mg.	PANTOTHENIC ACID	3.0 mg.
*IRON	12 mg.	PYRIDOXINE	0.6 mg.
MAGNESIUM	120 mg.	*RIBOFLAVIN	2.0 mg.
MANGANESE	0.4 mg.	*THIAMINE	1.2 mg.
*PHOSPHORUS	940 mg.	*VITAMIN A	3200 I.U.
POTASSIUM	1300 mg.	VITAMIN B_{12}	0.005 mg.
SODIUM	560 mg.	*VITAMIN D	420 I.U.
ZINC	2.6 mg.		

*PROTEIN (biologically complete)	32 Gm.
*CARBOHYDRATE	65 Gm.
*LIPIDS	30 Gm.

*Nutrients for which daily dietary allowances are recommended by the National Research Council

'FEOJECTIN' vs. BLOOD TRANSFUSION



Here you see a comparison of blood responses in two infants of the same age who happened to be hospitalized on the same day for severe iron-deficiency anemia. One infant was given 100 mg. of 'Feojectin' daily for three days, while the other was given two blood transfusions, one of 200 cc. and a second of 100 cc. on successive days.

From these results, Dickstein et al. suggest that, in selected situations, 'Feojectin' (saccharated iron oxide) can serve as an alternative to blood transfusions.

Am. J. Dis. Child. 84:52 (July) 1952.

FEOJECTIN*

the rapid-action, effective intravenous iron

Smith, Kline & French Laboratories, Philadelphia

Each 5 cc. 'Feojectin' ampul contains the equivalent of 100 mg. elemental iron.

★T.M. Reg. U.S. Pat. Off.

NOW
for the first time
full
therapeutic
dosage
of aminophylline
ORALLY

Cardalin tablets
PATENT PENDING

Cardalin-Phen tablets
PATENT PENDING

with safety and simplicity

for the cardiac patient
for the asthmatic patient
for diuresis

Cardalin
PATENT PENDING
tablets

Each tablet contains:

Aminophylline	5.0 gr.
Aluminum Hydroxide	2.5 gr.
Ethyl Aminobenzoate	0.5 gr.

Cardalin-Phen contains, in addition, ¼ gr. of phenobarbital for sedation.

Cardalin and Cardalin-Phen tablets are best tolerated after meals and preferably administered with one-half glassful of milk.

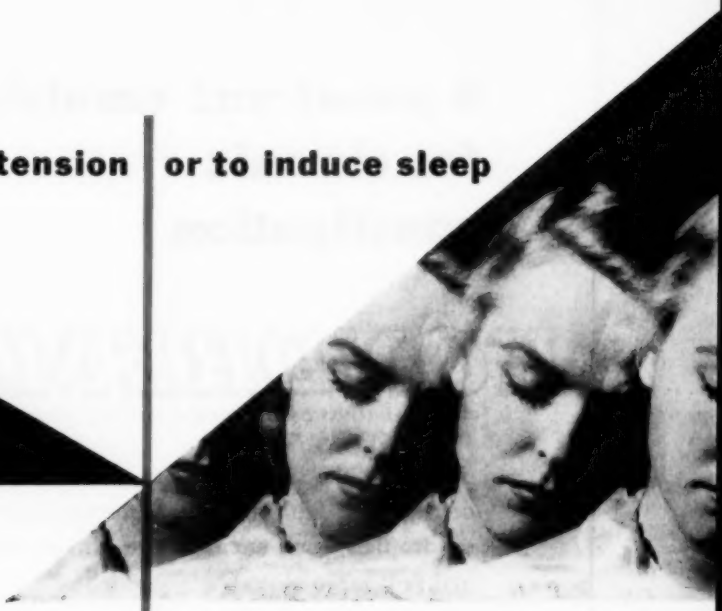
Supplied: Bottles of 100, 500, 1000.

Cardalin and Cardalin-Phen contain 5 grains of Aminophylline per tablet... the highest concentration supplied for Oral Administration. Two protective factors (Aluminum Hydroxide and Ethyl Aminobenzoate) counteract the local gastric irritation so common to oral aminophylline therapy. Prolonged treatment at high dosage levels can be accomplished with Cardalin and Cardalin-Phen, as demonstrated by extensive clinical studies.

Cardalin and Cardalin-Phen tablets rapidly produce clinical response of the same magnitude as that obtained by intravenous administration of aminophylline. These new products permit the physician to institute and maintain effective oral treatment in conditions formerly considered amenable only to rectal or parenteral aminophylline therapy.

IRWIN, NEISLER & COMPANY
Decatur, Illinois
Research to Serve Your Practice

to reduce tension | **or to induce sleep**



CARBRITAL®

calms the restless...rests the sleepless

CARBRITAL is invaluable for reducing daytime tension or inducing prompt, refreshing sleep at night. It combines the hypnotic action of sodium pentobarbital, plus the milder hypnotic but more prolonged sedative effect of carbromal. With **CARBRITAL**, patients relax easily, fall asleep quickly, and awaken refreshed and alert.

CARBRITAL is useful in a wide variety of indications including insomnia, nervous tension, and preoperative or obstetrical preparation.

Each CARBRITAL KAPSEAL (Full-strength) contains:	
Pentobarbital sodium	1½ grains
Carbromal	4 grains
Each CARBRITAL KAPSEAL (Half-strength) contains:	
Pentobarbital sodium	¾ grain
Carbromal	2 grains
Each fluidounce of CARBRITAL ELIXIR contains:	
Pentobarbital sodium	2 grains
Carbromal	6 grains

CARBRITAL KAPSEALS, full or half-strength, may be taken by adults in doses of one or more, on schedules determined by the physician. Children may be given ½ to 1 teaspoonful of CARBRITAL ELIXIR; adults 1 to 2 teaspoonfuls or more as required.

MEDICAMENTA VERA

Parke, Davis + Company

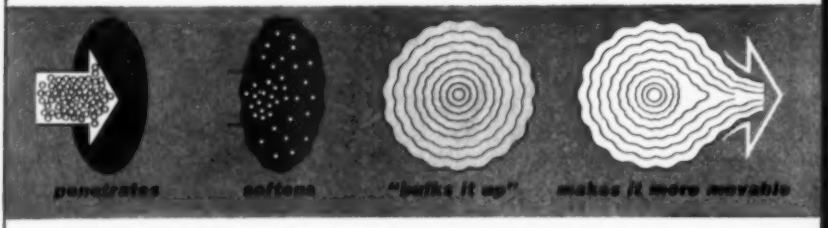
DETROIT, MICHIGAN

a *penetrant* emulsion for chronic constipation

KONDREMUL® (PLAIN)

COLLOIDAL EMULSION OF MINERAL OIL AND IRISH MOSS

permeates the hard, stubborn stool of chronic constipation with millions of microscopic oil droplets, each encased in a film of Irish moss... makes it more movable



KONDREMUL PATCH

KONDREMUL *(Plain)*—Pleasant-tasting and non-habit-forming. Contains 55% mineral oil. Supplied in bottles of 1 pt.

KONDREMUL *(With Cascara)*—0.66 Gm. nonbitter Ext. Cascara per tablespoon. Bottles of 14 fl.oz.

KONDREMUL *(With Phenolphthalein)*—0.13 Gm. phenolphthalein (2.2 gr.) per tablespoon. Bottles of 1 pt.

When taken as directed before retiring, KONDREMUL does not interfere with absorption of essential nutrients.

THE E. L. PATCH CO. — STONEHAM, MASSACHUSETTS

a single.

soluble

sulfonamide —

Gantrisin is especially soluble at the pH of the kidneys. That is why it is so well tolerated...does not require alkalies...does not cause renal blocking. There are over one hundred references to Gantrisin® in recent clinical literature.

For

meningitis —

...for severe infections...whenever oral therapy is not feasible...Gantrisin Diethanolamine Solution (40%, pH 7.4) may be given intramuscularly or intravenously <u>without</u> dilution. Also tablets and syrup.

FACTS *concerning*

neodrol

an important new agent

for suppressing mammary cancer

NEODROL* (stanolone-Syntex, androstane-17(β)-ol-3-one) is a new synthetic steroid complex with pronounced anti-tumor and anabolic activity.

In arresting soft-tissue lesions, NEODROL is markedly superior to testosterone, and at least its equal in arresting osseous metastases. Unlike testosterone, NEODROL is distinguished by its remarkable freedom from masculinizing effects.

In 42 cases of inoperable breast carcinoma, Escher, Farrow, *et al.*[1] report *symptomatic* improvement in 87% of cases. Under exceptionally severe criteria, positive *objective* improvement was obtained in 43%. "Marked" hirsutism and hoarseness were observed only once each; marked acne twice; marked increase in libido and clitoral hypertrophy not at all.

NEODROL is administered intramuscularly. Presently recommended dosage for mammary cancer is 100 mg. (2 cc.) 3 to 6 times weekly; for protein anabolic effect, 50 mg. (1 cc.) 3 to 6 times weekly.

NEODROL is a research development of SYNTEX, S. A. (Mexico) – pioneers in steroid hormone research and synthesis. It is being made available to the American medical profession through the facilities of Foundation Laboratories.

NEODROL may now be obtained through your usual source of supply in vials of 10 cc., 50 mg. per cc. *For complete information, please write to*

Syntex

FOUNDATION LABORATORIES, INC.

22 EAST 40TH STREET, NEW YORK 16, NEW YORK

1. A STUDY OF FORTY-TWO CASES OF ADVANCED MAMMARY CARCINOMA TREATED WITH ANDROSTANOLONE (STANOLONE) THERAPY (PRESENTED AT AMERICAN FEDERATION FOR CLINICAL RESEARCH, SOUTHERN SECTION, NEW ORLEANS, LA., JAN. 30, 1953). IN PRESS.

*TRADEMARK

*Salt is what makes things taste bad when it isn't in them.**

Most people find foods unappealing and insipid without salt. Therefore, when salt restriction is indicated, the patient must be impressed with the importance of a salt-free diet and must adhere faithfully to a rigid regimen. "With the development of such preparations as Neocurtasal . . . the problem of palatability and a salty taste has been fairly well solved . . ."[1]

Neocurtasal®

"*. . . trustworthy nonsodium-containing salt substitute*"[2]

—lends the desired salty flavor to foodstuffs, and can be used in all salt-free and low sodium diets.

CONSTITUENTS: Potassium chloride, ammonium chloride, potassium formate, calcium formate, magnesium citrate and starch.

and

NEOCURTASAL

Iodized

(contains potassium iodide 0.01%)

Neocurtasal looks and pours like table salt and may be used in the same manner.

Both available in 2 oz. shakers and 8 oz. bottles.

Winthrop-Stearns INC.

NEW YORK 18, N. Y. WINDSOR, ONT.

1. Merryman, M. P.: The Use of the Low Sodium Diet. *South Dakota Jour. Med. & Pharm.*, 2:57, Feb., 1949.
2. Heller, E. M.: The Treatment of Essential Hypertension. *Canad. Med. Assn. Jour.*, 61:293, Sept., 1949.

*Author unidentified. From Mencken, H. L.: A New Dictionary of Quotations, New York, Alfred A. Knopf, 1942, p. 1057.

maalox®

for gastric hyperacidity in peptic ulcer

Suspension MAALOX—Rorer provides the *hydroxides* of Magnesium and Aluminum in colloidal form . . . pleasantly flavored and highly acceptable, even with prolonged use. Relief of pain and epigastric distress is prompt and long-lasting. Freedom from constipation and side effects common to other antacids is noteworthy.

supplied:

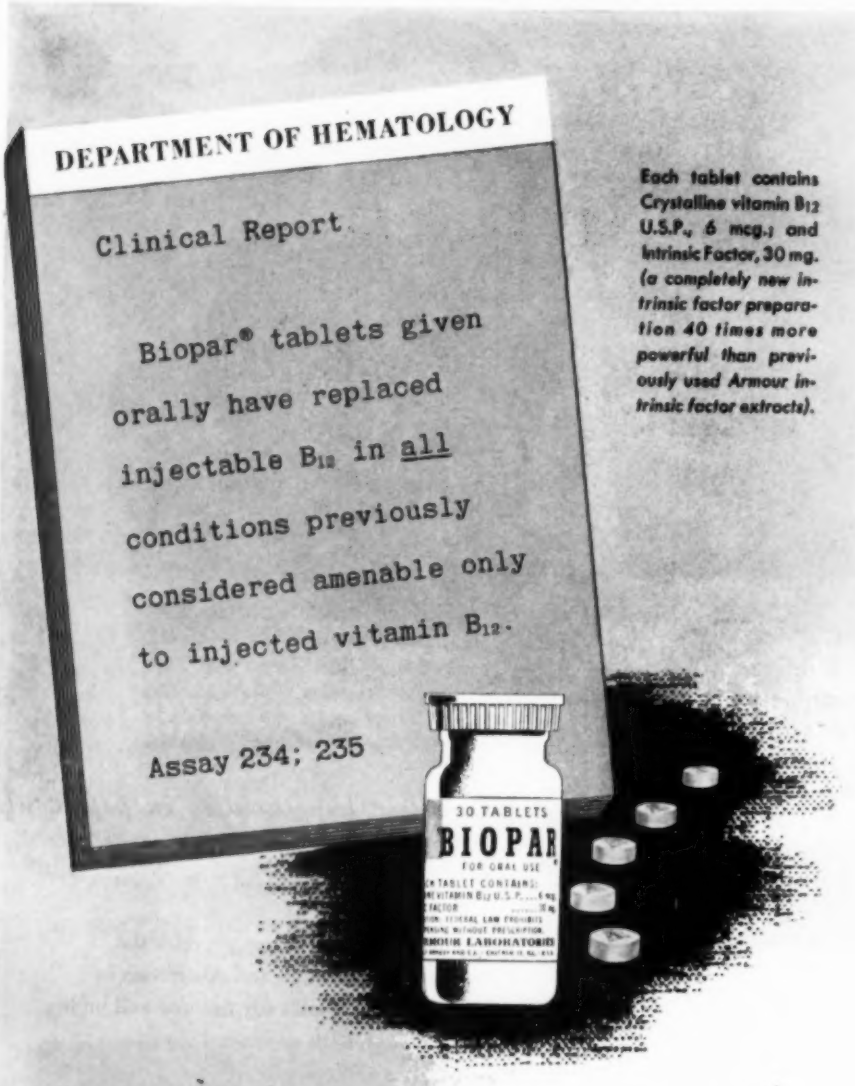
in 355 cc. (12 fluidounce) bottles. Also in bottles of 100 tablets. (Each Maalox tablet is equivalent to 1 fluidram of Suspension.)

Samples will be sent promptly upon request.

WILLIAM H. RORER, INC.

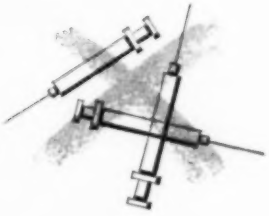
Drexel Bldg., Independence Square, Philadelphia 6, Penna.

ESTABLISHED IN 1910

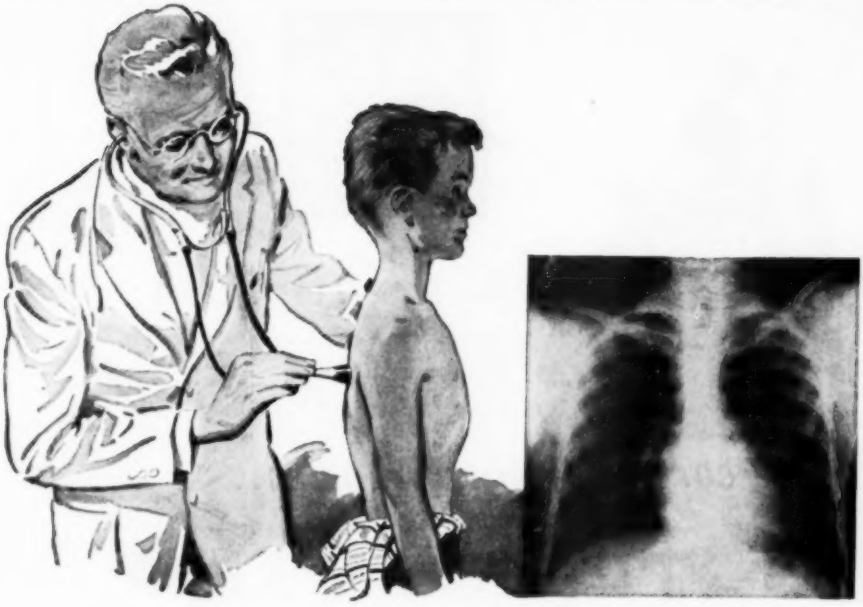

DEPARTMENT OF HEMATOLOGY
Clinical Report
Biopar® tablets given orally have replaced injectable B_{12} in all conditions previously considered amenable only to injected vitamin B_{12}.
Assay 234; 235
30 TABLETS
BIOPAR
FOR ORAL USE
ARMOUR LABORATORIES

Each tablet contains Crystalline vitamin B_{12} U.S.P., 6 mcg.; and Intrinsic Factor, 30 mg. *(a completely new intrinsic factor preparation 40 times more powerful than previously used Armour intrinsic factor extracts).*

Biopar tablets are therapeutically equivalent orally (in the dosage range employed) to parenteral vitamin B_{12}. Supplied in bottles of 30.



THE ARMOUR LABORATORIES
A DIVISION OF ARMOUR AND COMPANY • CHICAGO 11, ILLINOIS
world-wide dependability
PHYSIOLOGIC THERAPEUTICS THROUGH BIORESEARCH



A drug of choice in tuberculosis

As therapeutically active as streptomycin, CRYSTALLINE DIHYDROSTREPTOMYCIN SULFATE MERCK is less toxic to the vestibular apparatus, minimizes pain and swelling on injection, and may be used even in some patients allergic to streptomycin.

This preferred product is available in dry powder form and in convenient ready-to-inject form as SOLUTION OF CRYSTALLINE DIHYDROSTREPTOMYCIN SULFATE MERCK.

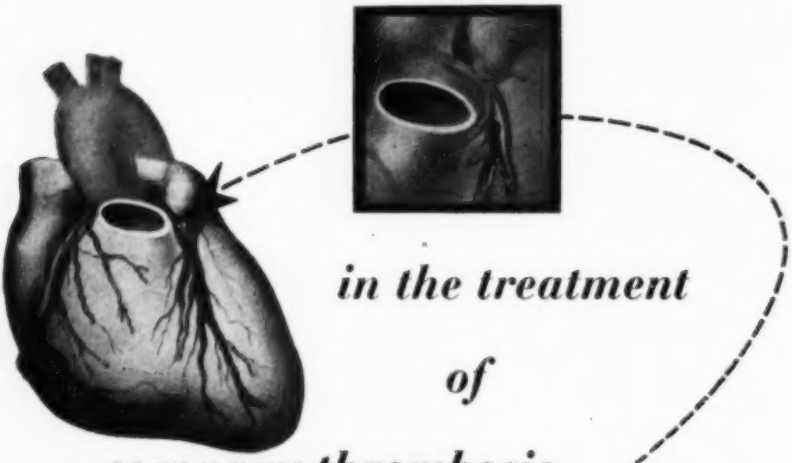
PARA-AMINOSALICYLIC ACID MERCK (PAS), when used in combination with CRYSTALLINE DIHYDROSTREPTOMYCIN SULFATE MERCK, prolongs the effective period of antibiotic therapy by inhibiting or delaying the development of bacterial resistance.

Crystalline Dihydrostreptomycin Sulfate Merck

COUNCIL ACCEPTED

Research and Production for the Nation's Health

MERCK & CO., INC.
Manufacturing Chemists
RAHWAY, NEW JERSEY
In Canada: MERCK & CO. Limited—Montreal



in the treatment

of

coronary thrombosis...

TROMEXAN®

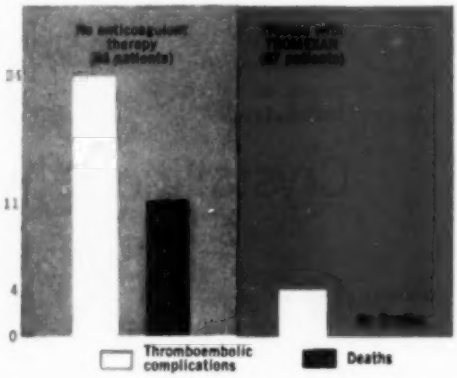
ethyl acetate

significantly reduces

mortality and complication rate...

The remarkable effectiveness of oral anticoagulant therapy with TROMEXAN in reducing mortality and complications of coronary thrombosis has been authoritatively substantiated.[1] The frequency of thromboembolic incidents fell "... from approximately one in every four patients in the control groups to less than one in twenty among the Tromexan-treated patients."[1] No deaths occurred among 87 patients treated with TROMEXAN.

In all forms of thromboembolic disease, TROMEXAN offers the advantages of more rapid action, lesser cumulation, and diminished risk of sustained or severe hemorrhage.



1. Tulloch, J. A., and Gilchrist, A. R.: Tromexan in the Treatment of Coronary Thrombosis, Am. Heart J. 42:864, 1951.

TROMEXAN® ethyl acetate (brand of ethyl biscoumacetate). Available as scored tablets of 300 mg. and 150 mg.

GEIGY PHARMACEUTICALS

Division of Geigy Company, Inc.
220 Church Street, New York 13, N. Y.
In Canada: Geigy (Canada) Limited, Montreal.

FOUR

FOR GREATER TOLERANCE

THE FIRST QUADRI-SULFA MIXTURE

DELTAMIDE

Composition:
Each Tablet or each teaspoon (5 cc.) Chocolate-flavored Suspension of Deltamide contains:

Sulfadiazine.....0.167 Gm.
Sulfamerazine.....0.167 Gm.
Sulfamethazine.....0.056 Gm.
Sulfacetamide.....0.111 Gm.

Each Tablet or teaspoon (5 cc.) of suspension provides 0.5 Gm. of total sulfonamides.

Supplied: Deltamide tablets in bottles of 100; Deltamide Suspension in 4 oz. and 16 oz. bottles.

Indicated in infections due to Group A hemolytic streptococci, staphylococci, pneumococci, meningococci, gonococci, and other microorganisms responsive to sulfonamides.

1. Lehr, D.: Brit. M. J.: 2: 543-548, 1948.
2. Lehr, D.: Brit. M. J.: 2: 601, 1950.
3. Hawking, F., and Lawrence, J. S.: The Sulfonamides, New York, Grune and Stratton, 1951.

DELTAMIDE—a quadruple sulfonamide tablet and suspension—represents the latest development in multiple sulfonamide therapy. Deltamide utilizes the fact that an increase in the number of sulfonamides in sulfonamide mixtures provides the significant advantages of greater clinical safety with lowered incidence of toxic and allergic reactions.[1, 2]

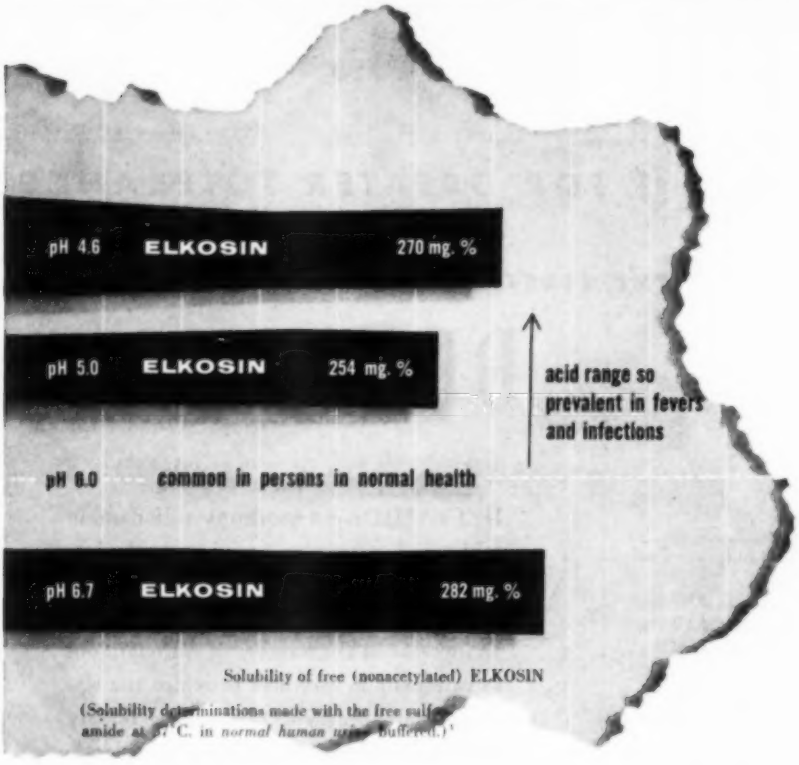
By combining four of the most useful sulfonamides,[3] Deltamide is superior on four counts:

- **Rapid initial absorption**
- **Effective blood levels**
- **High urinary solubility**
- **Very low toxicity**

THE ARMOUR LABORATORIES
A DIVISION OF ARMOUR AND COMPANY · CHICAGO 11, ILLINOIS

world-wide dependability

PHYSIOLOGIC THERAPEUTICS THROUGH BIORESEARCH


pH 4.6 ELKOSIN 270 mg. %
pH 5.0 ELKOSIN 254 mg. %
acid range so prevalent in fevers and infections
pH 8.0 common in persons in normal health
pH 6.7 ELKOSIN 282 mg. %
Solubility of free (nonacetylated) ELKOSIN

high solubility where it counts

in the acid pH range
so prevalent in fevers
and infections

alkalis not needed

ELKOSIN®

SULFADIMETINE CIBA

a new advance in sulfonamide safety

tablets 0.5 Gm., double-scored. Bottles of 100 and 1000
suspension in syrup 0.25 Gm. per teaspoonful (4 cc.). Pints.

1. Ziegler, J. B.; Bagdon, R. E., and Shabica, A. C.: To be published.

Ciba

Can FUNCTIONAL G. I. SPASM
be relieved . . . without
"BELLADONNA BACKFIRE"?

YES!

More and more published clinical studies continue to prove that BENTYL provides effective relief from pain, cramps and general discomfort due to functional G.I. spasm . . . without "belladonna backfire."

℞ BENTYL

SAFE, DOUBLE-SPASMOLYSIS

Another product of research by
Merrell
SINCE 1828
Prescription pharmaceuticals for 135 years
New York • CINCINNATI • St. Thomas, Ont.

Trade-mark "Bentyl" Hydrochloride

Each capsule or teaspoonful syrup contains
BENTYL 10 mg.
when sedation is desired
BENTYL 10 mg.
WITH PHENOBARBITAL 15 mg.

DOSAGE:
Adults—2 capsules or 2 teaspoonfuls syrup 3 times daily, before or after meals. If necessary repeat dose at bedtime.
In Infant Colic—½ to 1 teaspoonful syrup 3 times daily before feeding.

℞

1. Antacid combination
2. Demulcent
3. Antispasmodic

Now you can add the

"MISSING FOURTH"

in peptic ulcer therapy

4. ANTILYSOZYME

KOLANTYL INCLUDES THE IMPORTANT 4th FACTOR

1. **A SUPERIOR ANTACID COMBINATION** (magnesium oxide and aluminum hydroxide, also a specific antipeptic).
2. **A SUPERIOR DEMULCENT** (methylcellulose, a synthetic mucin).
3. **A SUPERIOR ANTISPASMODIC** (BENTYL Hydrochloride) which provides direct smooth muscle and parasympathetic depressant qualities without "belladonna backfire."
4. **INACTIVATION OF LYSOZYME**—Laboratory research and clinical studies 1,2 indicate that lysozyme plays an important role as one of the etiologic agents of peptic ulcer. By inhibiting or inactivating lysozyme with sodium lauryl sulfate, KOLANTYL includes the important 4th factor toward more complete control of peptic ulcer.

KOLANTYL

DOSAGE: 2 Kolantyl tablets or 2 to 4 teaspoonfuls of Kolantyl Gel every 3 hours as needed for relief.

1. Hufford, A. R., Rev. of Gastroenterology, 18:588, 1951
2. Miller, B. N., J. So. Carolina M. A., 48:1, 1952

TRADE-MARKS "KOLANTYL," "BENTYL"

Another product of research by

Merrell
SINCE 1828

Prescription pharmaceuticals for 125 years
New York • CINCINNATI • St. Thomas, Ont.

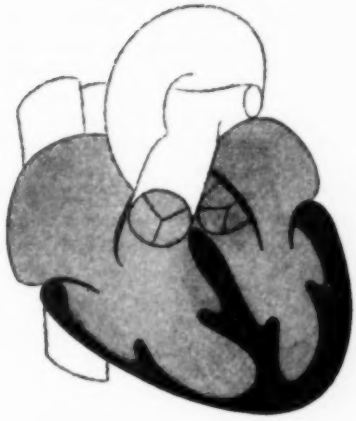
TRADE-MARKS
"KOLANTYL,"
"BENTYL"

NOW

the first intramuscular digitoxin

DIGITALINE NATIVELLE® INTRAMUSCULAR

for dependable digitalization and maintenance when the oral route is unavailable



DIGITALINE NATIVELLE INTRAMUSCULAR is indicated for patients who are comatose, nauseated or uncooperative, or whose condition precludes the use of the oral route.

DIGITALINE NATIVELLE INTRAMUSCULAR provides all the unexcelled virtues of its parent oral preparation.

Steady, predictable absorption.

Equal effectiveness, dose-for-dose with oral DIGITALINE NATIVELLE.

Easy switch-over to oral medication.

Clinical investigation has shown that DIGITALINE NATIVELLE INTRAMUSCULAR is "effective in initiation and maintenance of digitalization. A satisfactory therapeutic effect was obtained with minimal local and no undesirable systemic effects."*

DIGITALINE NATIVELLE INTRAMUSCULAR – 1-cc. and 2-cc. ampules, boxes of 6 and 50. Each cc. provides 0.2 mg. of the original digitoxin – DIGITALINE NATIVELLE.

*Strauss, V.; Simon, D. L.; Iglauer, A., and McGuire, J.: Clinical Studies of Intramuscular Injection of Digitoxin (Digitaline Nativelle) in a New Solvent, Am. Heart J. 44:787, 1952.

Literature and samples available on request.

VARICK PHARMACAL COMPANY, INC.
(Division of E. Fougera & Co., Inc.)
75 Varick Street, New York 13, N. Y.

for low-sodium dieters

de gustibus...

By direct appeal to the palate, DIASAL enlists the willing cooperation of patients on low-sodium diets. Its exceptionally high taste-equivalence to table salt is matched by close resemblance in other properties[1]—DIASAL looks, pours and otherwise behaves like sodium chloride at the table and in the kitchen.

Containing chiefly potassium chloride (plus glutamic acid and inert excipients), DIASAL is free from sodium, lithium and ammonium. It is accordingly safe to prescribe for prolonged and liberal use. DIASAL also serves as a prophylactic against the potassium depletion which may accompany low-sodium dieting.[2]

DIASAL FOUGERA

seasons food like salt safely

packaging: available in 2-oz. shakers and 8-oz. bottles.

Samples and low-sodium-diet sheets for your patients available on request to Professional Service Department.

FOUGERA **E. FOUGERA & COMPANY, INC.**
75 VARICK STREET, NEW YORK 13, N. Y.

1. Rimmerman, A. B., and others: A Comparative Study of Sodium-free Salt Substitutes. Am. Pract. & Digest Treat. 2:168, 1951.
2. Fremont, R. E., and others: Postgrad. Med. 10:216, 1951.

Upjohn

mixed surface infections . . .

Each gram contains 5 mg. neomycin sulfate (equivalent to 3.5 mg. neomycin base).

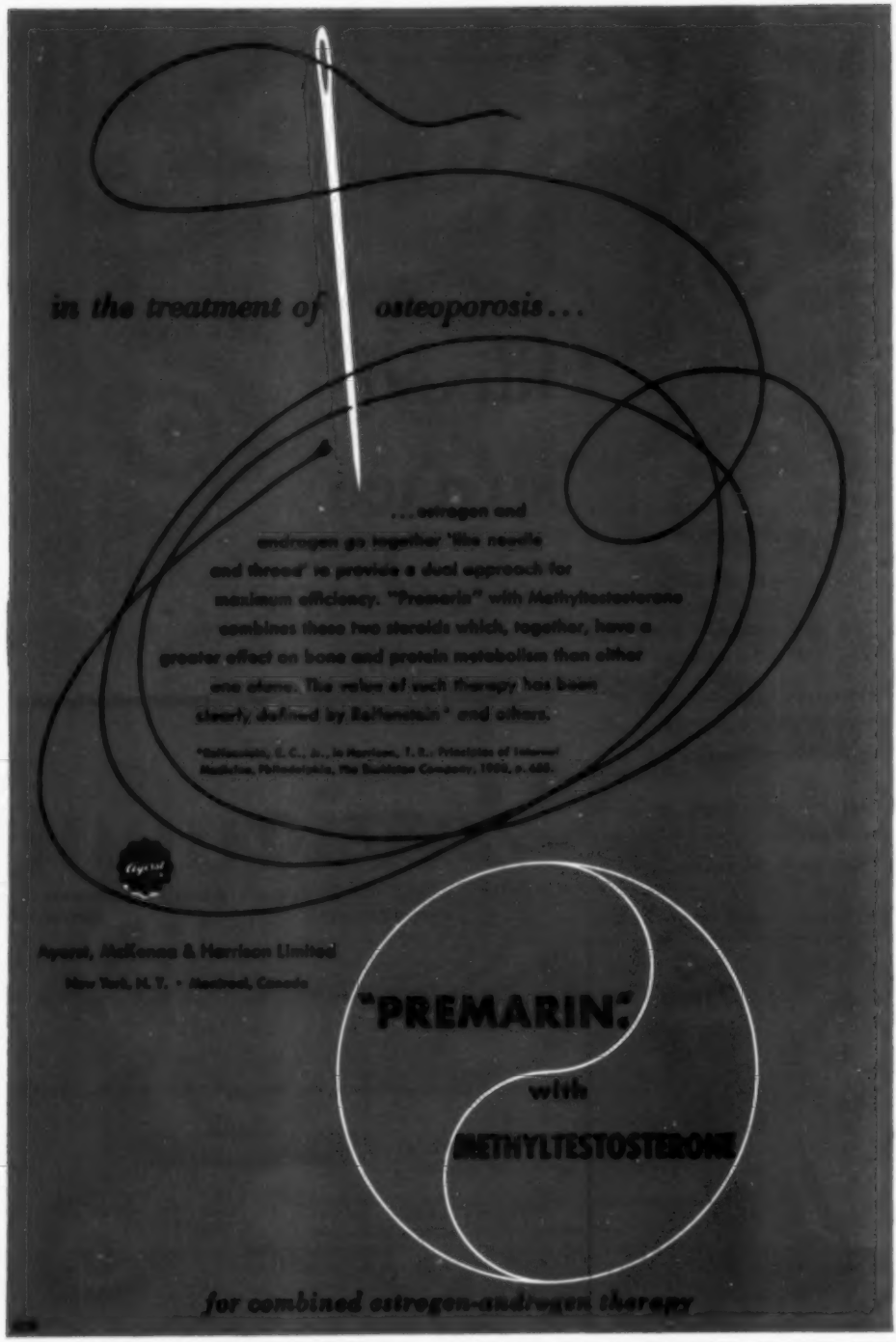
Available: Ointment in ½ oz. and 1 oz. tubes, and 4 oz. jars. Cream in ½ oz. tubes.

The Upjohn Company, Kalamazoo, Michigan

Myciguent

Trademark Reg. U. S. Pat. Off.

CREAM OR OINTMENT


in the treatment of osteoporosis...
...estrogen and
androgen go together 'like needle
and thread' to provide a dual approach for
maximum efficiency. "Premarin" with Methyltestosterone
combines these two steroids which, together, have a
greater effect on bone and protein metabolism than either
one alone. The value of such therapy has been
clearly defined by Reifenstein* and others.
*Reifenstein, E. C., Jr., in Harrison, T. R.: Principles of Internal
Medicine, Philadelphia, The Blakiston Company, 1950, p. 685.
Ayerst, McKenna & Harrison Limited
New York, N. Y. • Montreal, Canada
"PREMARIN"
with
METHYLTESTOSTERONE
for combined estrogen-androgen therapy

following anorectal surgery . . .

". . . more rapid postoperative healing as compared with patients on mineral oil"[1]

Cantor[1] concludes—after studying 400 patients, equally apportioned between mineral oil and refined psyllium therapy—that L.A. Formula accelerates healing as much as 2 to 4 weeks compared with patients taking mineral oil for the management of postoperative constipation following anorectal surgery. This is due, he states, to the clean wound area which L.A. Formula leaves for the better development of granulation tissue.

Cantor notes these additional advantages of L.A. Formula therapy. L.A. Formula provides an internal dilator action which acts to prevent adhesions, stricture and stenosis. Patients find L.A. Formula palatable and easy to take and do not become habituated to its use. Its laxative action is dependable.

He concludes that L.A. Formula "provides a natural, unabsorbable bulk and lubricant with no clinical disadvantages. It offers many advantages over mineral oil and has none of mineral oil's disadvantages." *Burton, Parsons & Company, Washington 9, D. C.*

Send for Samples for Clinical Appraisal

1. Cantor, A. J., Am. J. Proctol. 3:204-210, (Sept.) 1952.

L. A. FORMULA

effective bulk producer • unsurpassed for palatability

THESODATE

THE ORIGINAL ENTERIC-COATED TABLET
OF THEOBROMINE SODIUM ACETATE

provides
EFFECTIVE
WELL-TOLERATED
PROLONGED
VASO-DILATION

REPEATEDLY SHOWN and proven by objective tests on human subjects[1] – this is one of the most effective of all the commonly known Xanthine derivatives. Because of the enteric coating it may be used with marked freedom from the gastric distress characteristic of ordinary Xanthine therapy. Thus THESODATE, with its reasonable prescription price also, enjoys a greater patient acceptability.

Available: In bottles of 100, 500, 1000.

TABLETS THESODATE

*(7½ gr.) 0.5 Gm. *(3¾ gr.) 0.25 Gm.

THESODATE WITH PHENOBARBITAL

*(7½ gr.) 0.5 Gm. with (½ gr.) 30 mg.
(7½ gr.) 0.5 Gm. with (¼ gr.) 15 mg.
*(3¾ gr.) 0.25 Gm. with (¼ gr.) 15 mg.

THESODATE WITH POTASSIUM IODIDE

(5 gr.) 0.3 Gm. with (2 gr.) 0.12 Gm.

THESODATE, POTASSIUM IODIDE WITH PHENOBARBITAL

(5 gr.) 0.3 Gm., (2 gr.) 0.12 Gm. with (¼ gr.) 15 mg.

*In capsule form also, bottles of 25 and 100.

1. Riseman, J. E. F. and Brown, M. G. Arch. Int. Med. 60: 100, 1937
2. Brown, M. G. and Riseman, J. E. F. JAMA 109: 256, 1937.
3. Riseman, J. E. F. N. E. J. Med. 229: 670, 1943.

in
CORONARY
ARTERY
DISEASE

For samples just send your Rx blank marked — 7THS

Brewer
EST. 1852

BREWER & COMPANY, INC. WORCESTER 8, MASSACHUSETTS U.S.A.

The demands of convalescence are high...

Trauma, infection, surgery and chronic illness all present visible or hidden tissue damage requiring protein for repair.

For sound protection against the "difficult convalescence" of protein depletion, supplement the diet with between-meal servings of—

Meritene®

FORTIFIED WHOLE PROTEIN SUPPLEMENT

Easy to mix...tastes good

More Protein-Rich than any Eggnog...and lower in cost†...

A MERITENE MILK SHAKE

the extra which only Meritene gives...

	*EGGNOG	MERITENE MILKSHAKE
Protein	12.5 Gm.	15.8 Gm.
Fat	12.6 Gm.	8.0 Gm.
Carbohydrate	17.7 Gm.	25.5 Gm.
Calcium	0.24 Gm.	0.5 Gm.
Phosphorus	0.27 Gm.	0.4 Gm.
Iron	1.5 mg.	4.4 mg.
Vitamin A	843 I.U.	1745 I.U.
Thiamine	0.12 mg.	0.7 mg.
Riboflavin	0.45 mg.	1.6 mg.
Niacin	0.2 mg.	6.4 mg.
Ascorbic Acid	2.0 mg.	26.4 mg.
Vitamin D	30 I.U.	150 I.U.
Calories	233	237

*Eggnog nutritive values from Bowes, A. de P., and Church, C. F.: Food Values of Portions Commonly Used, Philadelphia, College Offset Press, 1951, Ed. 7.

†Based on 25 lb. institutional size can.

Free...

MERITENE DIET SERVICE

offers the following diets:

1. restricted sodium
2. low-cholesterol • limited-fat
3. bland low-cellulose
4. ulcer
5. diabetic
6. diseases of the liver and gallbladder

—as if your secretary had just typed them.

1 lb. and 5 lb. cans... plain or chocolate flavor

MI 53

THE DIETENE COMPANY
3117 Fourth Avenue South, Minneapolis 8, Minn.

Please send me free clinical sample of Meritene and the free sample diet sheets.

M. D.

ADDRESS

CITY ZONE STATE

Here is an electrocardiograph built to provide the continuity of service you have a right to expect

While it is important that your ECG be Accepted by the AMA Council on Physical Medicine and Rehabilitation, it is of equal and perhaps greater consequence to you that it also be designed and constructed to *maintain these performance standards in continuous service.*

The VISO-CARDIETTE is designed first of all to *exceed* the Council's requirements concerning the instrument's recording characteristics. And then, the *highest quality* purchasing and production control assures the maintaining of that performance *in each instrument* long after it has left the factory.

For example, all purchased components selected for use in the Viso are of *precision instrument quality,* and all are chosen for their *continuity of service* rather than their initial cost. Also, every component in each assembly and every assembly in each instrument, as well as the complete instrument itself, are all *thoroughly checked to rigid Sanborn specifications* as they move along the production line.

In addition, VISO-CARDIETTE construction is guided by electronic and mechanical experts who know from long experience that electrocardiography demands an instrument of *only* the highest quality performance.

Yes, you can expect Continuity of Service with a VISO-CARDIETTE.

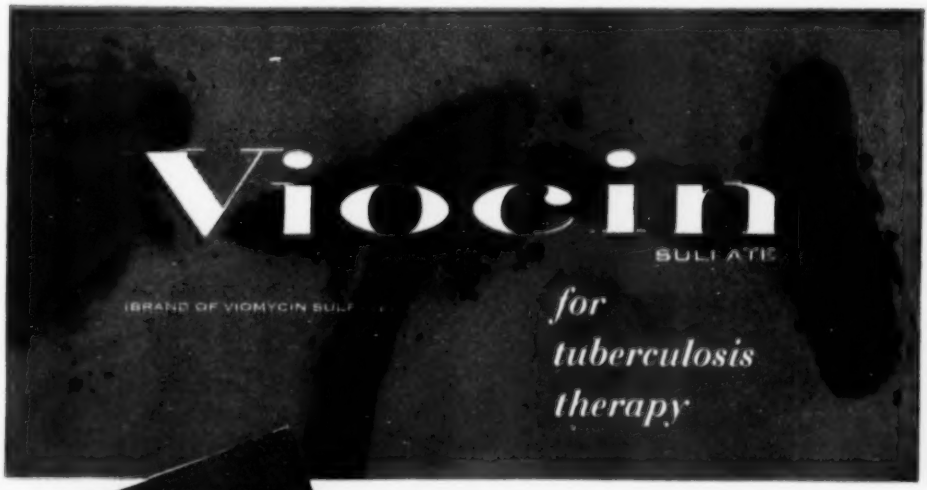
A new booklet, "Check Lists for Buyers of ECG's" offers guidance in evaluating the various instruments available. A copy will be sent simply on your request.

Makers of fine ECG's since 1924

Sanborn Company

CAMBRIDGE 39, MASSACHUSETTS

a new achievement of *Pfizer* research



now released for clinical use

From the research laboratories of the world's largest producer of antibiotics comes Viocin — a new antibiotic with important activity against *Mycobacterium tuberculosis.*

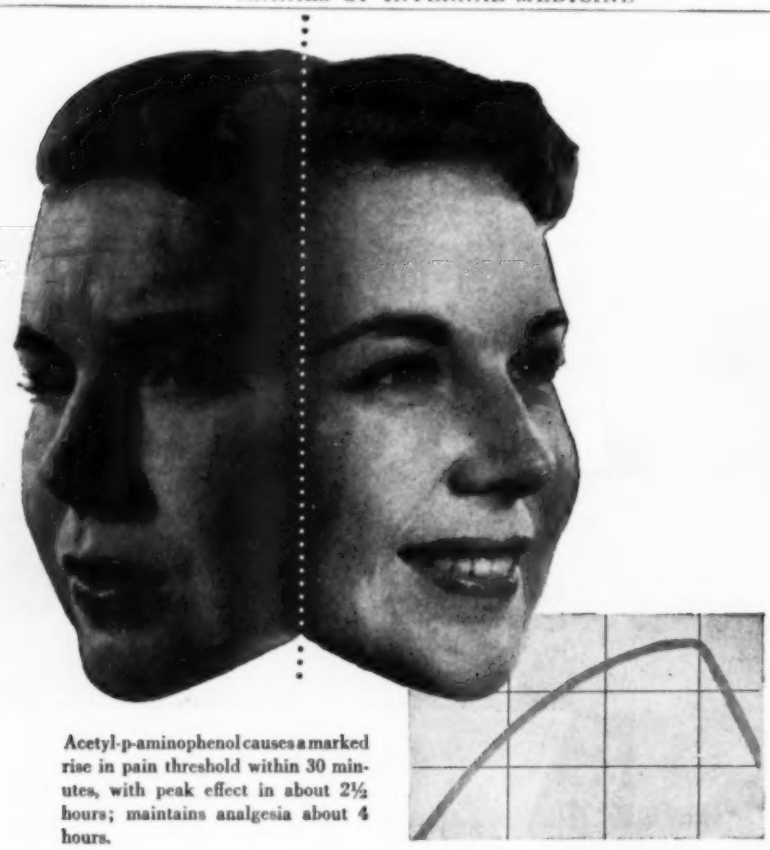
A pioneer in the development of streptomycin, dihydrostreptomycin and isoniazid, Pfizer thus adds another powerful agent to the modern management of tuberculosis.

Viocin therapy will be particularly valuable when other medication cannot be used, and as an adjunctive measure in serious, progressive tuberculosis and many cases of extrapulmonary tuberculosis.

Viocin is supplied as the sulfate, for intramuscular injection.

For further details, see your Pfizer Professional Service Representative.

Pfizer ANTIBIOTIC DIVISION • CHAS. PFIZER & CO., INC.
BROOKLYN 6, N.Y.



Acetyl-p-aminophenol causes a marked rise in pain threshold within 30 minutes, with peak effect in about 2½ hours; maintains analgesia about 4 hours.

NEW ANALGESIC RAISES PAIN THRESHOLD 26%

Trigesic provides the advantages of acetyl-p-aminophenol, fast-acting analgesic, plus the benefits of aspirin and caffeine. Trigesic is an exceptional analgesic that has a three-fold action for the patient's comfort: analgesic, antipyretic, sedative. Bottles of 100 and 1,000.

TRIGESIC

Squibb Analgesic Compound

Per Tablet:

acetyl-p-aminophenol	0.125 Gm. (2 gr.)
aspirin	0.23 Gm. (3½ gr.)
caffeine	0.03 Gm. (½ gr.)

Trigesic with Codeine contains 8 mg. (⅛ gr.), 16 mg. (¼ gr.), 32 mg. (½ gr.) or 65 mg. (1 gr.) codeine phosphate.

'Trigesic' is a registered trademark

SQUIBB

Why Obedrin

. . . for the obese patient?

Because

Obedrin offers a practicable solution to the problem of keeping an obese patient on a restricted diet.

Because

Thousands of enthusiastic physicians have found that Obedrin curbs the appetite without making the patient jittery and does not cause insomnia.

Because

Obedrin contains enough vitamins to supplement the restricted diet. A large dose of vitamin C is included to help mobilize tissue fluids.

Because

Obedrin contains *Pento*barbital, a short-acting barbiturate, as a corrective. Pentobarbital has approximately the same duration of action as methamphetamine, so the possibility of cumulative barbiturate effect is negligible.

Available: The 60-10-70 Diet.* This is a convenient, variable diet, with enough roughage to eliminate necessity of artificial bulk laxatives.

Write for Pads of daily Menus of the 60-10-70 Diet* and professional sample of Obedrin

Each Obedrin tablet contains:

Semoxydrine HCl (Methamphetamine HCl)	5 mg.
Pentobarbital	20 mg.
Ascorbic Acid	100 mg.
Thiamine HCl	0.5 mg.
Riboflavin	1 mg.
Niacin	5 mg.

THE S. E. MASSENGILL COMPANY • BRISTOL, TENN.

DISTINGUISHED DIPLOMAT

... Dietary Dub

Each SUR-BEX Tablet contains:

Thiamine Mononitrate	6 mg.
Riboflavin	6 mg.
Nicotinamide	30 mg.
Pyridoxine Hydrochloride	1 mg.
Vitamin B_{12} (as vitamin B_{12} concentrate)	2 mcg.
Pantothenic Acid (as calcium pantothenate)	10 mg.
Liver Fraction 2, N.F.	0.3 Gm. (5 grs.)
Brewer's Yeast, Dried	0.15 Gm. (2½ grs.)

SUR-BEX WITH VITAMIN C contains 150 mg. of ascorbic acid in addition to the vitamin B complex factors.

FOR all his worldly finesse, he's a bungler in his own dietary affairs. Soon, he'll be negotiating for a corrected diet plus a potent, nutritional supplement such as SUR-BEX or SUR-BEX WITH VITAMIN C.

Each compressed, easy-to-swallow SUR-BEX tablet provides six B complex factors, liver fraction and brewer's yeast. Also, SUR-BEX + C offers five times the minimum daily requirement of ascorbic acid.

No trace of liver odor. Vanilla-flavored, triple coating. Daily prophylactic dose, one tablet; two or more for severe deficiencies. All pharmacies in bottles of 100, 500 and 1000. Abbott

PRESCRIBE

Sur-bex® or Sur-bex + C

(Abbott's Vitamin B Complex Tablets)

Made from the *leaf*—

Always
WAS, IS and
WILL BE
Dependable
in digitalization
and its maintenance

The physician
can always
rely on

Pil. Digitalis (Davies, Rose)
0.1 Gram (approx. 1½ grains)

These certain qualities can be positively identified

Comprise the entire properties of the leaf of Digitalis

Physiologically Standardized

Each Pill is equivalent to one U. S. P. Digitalis Unit

Clinical samples and literature sent to physicians on request

Davies, Rose & Company, Limited Boston 18, Mass.

PHARMACEUTICAL MANUFACTURERS

D23

sodium restriction without malnutrition

Protein deficiency may develop to a serious degree in patients on prolonged low-sodium diets, since the foods high in animal protein (e.g., meat, eggs, milk and cheese) are high in sodium also. Lonalac® safeguards protein adequacy of the low-sodium diet by supplying the protein equivalent of milk, with a negligible amount of sodium.

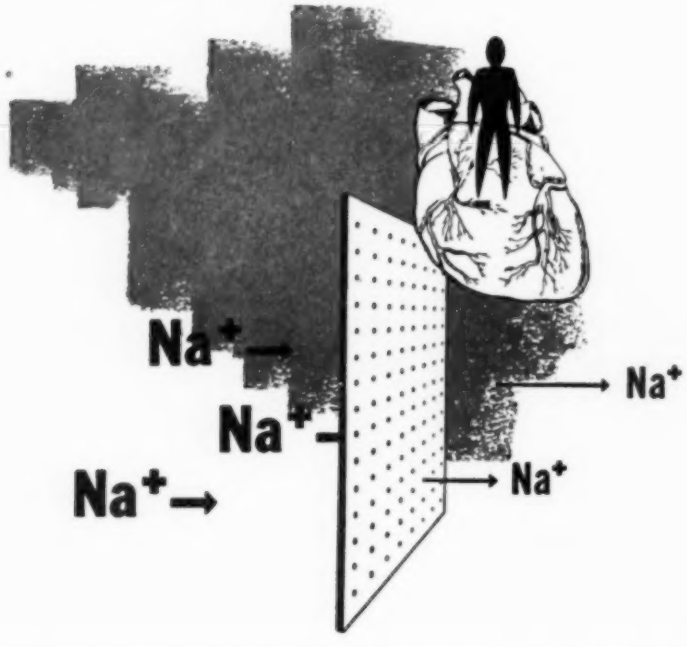
Lonalac is easily reconstituted with water . . . combines well with other foods to provide varied and nutritionally adequate diets containing as little as 200 mg. sodium.

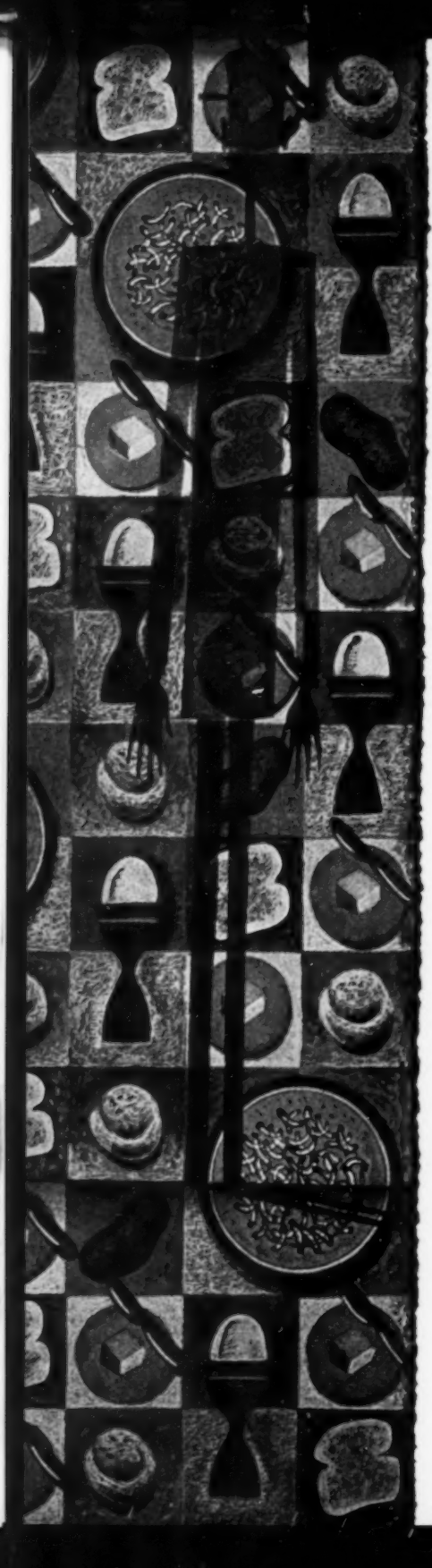
Flexible low-sodium diet outlines with Lonalac recipes are available on request.

Lonalac

MEAD JOHNSON & COMPANY
Evansville 21, Ind., U.S.A.

MEAD





for caloric boost
without gastric burden
...when weight gain
is the objective

EDIOL

TRADEMARK

[ORAL FAT EMULSION SCHENLEY]

Just 2 tablespoonfuls of EDIOL* oral fat emulsion q.i.d. add 600 extra calories to the daily diet without increasing bulk intake or blunting the appetite for essential foods. This EDIOL regimen is the caloric equivalent of:

6 servings of macaroni and cheese, or
1 dozen Parker House rolls, or
12 pats of butter, or
8 boiled eggs, or
6 baked potatoes, or
9½ slices of bread

EDIOL is an exceptionally palatable, creamy emulsion of coconut oil (50%) and sucrose (12½%). The unusually fine particle size of EDIOL (average, 1 micron) favors ease of digestion and rapid assimilation. For children, or when fat tolerance is a problem, small initial dosage may be prescribed, then increased to the level of individual tolerance.

Available through all pharmacies, in bottles of 16 fl.oz.

schenley

SCHENLEY LABORATORIES, INC.
LAWRENCEBURG, INDIANA

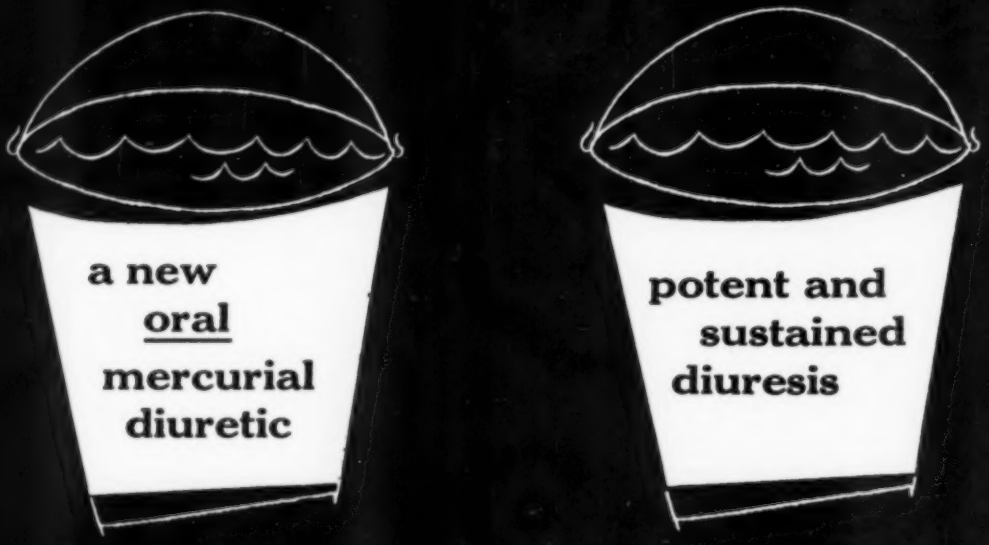
©Schenley Laboratories, Inc.

*Trademark of Schenley Laboratories, Inc.

ACCEPTED
COUNCIL ON PHARMACY AND CHEMISTRY
AMERICAN MEDICAL ASSOCIATION

CUMERTILIN®

[Brand of Mercumatilin]



Samples? Just write to:

ENDO PRODUCTS INC., RICHMOND HILL 18, N. Y.

Tablets

Endo®

CUMERTILIN tablets have been administered for prolonged periods with little or no gastrointestinal irritation

CUMERTILIN tablets produce a very satisfactory diuresis, reducing existent edema and retarding the reaccumulation of fluids in the tissue.

CUMERTILIN tablets eliminate the need for injections in certain cases, and markedly lengthen the interval between injections in others. Signs of cardiac failure were controlled with CUMERTILIN tablets in a series of ambulant patients, after cardiac compensation had been achieved with parenteral mercurials.

INDICATIONS: Congestive heart failure; salt retention edema and ascites; hypertensive and arteriosclerotic cardiovascular disease resulting in myocardial decompensation; dyspnea and pleural effusion of cardiac origin; in carefully selected cases of nephrosis, subacute and chronic nephritis; to permit freer fluid and salt intake; to maintain a more stable fluid and sodium balance.

DOSAGE: 1 to 3 tablets daily, as required.

Supplied as orange sugar-coated tablets each containing 67.7 mg. CUMERTILIN (equivalent to 20 mg. each of mercury and theophylline). Also available as CUMERTILIN Sodium Injection, 1- and 2-cc. ampuls, 10-cc. vials.

"We...give Depropanex routinely to all our patients following operations"[1]

When DEPROPANEX *is used routinely following abdominal surgery, "Rarely do we resort to the nasal suction apparatus, and since there is very little vomiting we do not need to resort to intravenous feedings."*[1]

Depropanex

SHARP & DOHME

DEPROTEINATED PANCREATIC EXTRACT

Non-narcotic Prevention or Relief of Pain due to Smooth Muscle Spasm.

DEPROPANEX has been widely employed for relief of renal and ureteral colic, and other painful conditions involving smooth muscle spasm. When administered following abdominal surgery, this physiologic agent is most effective in maintaining "uniformly good tone to the bowel all through the postoperative period."[1]

In the treatment of intermittent claudication, "if adequate doses of DEPROPANEX do not increase the distance which the patient can walk before he has pain it is improbable that anything will."[2]

DEPROPANEX is non-narcotic and nontoxic. Unlike morphine, which simply blocks cerebral recognition of pain, DEPROPANEX acts directly on smooth muscle tissue. It is a deproteinated saline solution of a chemically derived, protein-free, nitrogenous fraction obtained from an acid-alcohol treatment of mammalian pancreas.

In renal colic, DEPROPANEX *alleviates both pain and spasm: "Relaxation of this spasm causes relief from pain and also restores the physiological normalcy in the ureter."*[3]

DEPROPANEX Deproteinated Pancreatic Extract is supplied in 10-cc. rubber-capped vials.

Sharp & Dohme, Philadelphia 1, Pa.

1. Heimark, J.J. and Parsons, R.L.: Minnesota Med., *33*:1102, 1950.
2. J.A.M.A., Queries and Minor Notes, *135*:810, 1947.
3. Carroll, G. and Zingale, F.G.: Southern Med. J., *31*:233 1938.

ANNALS OF
INTERNAL MEDICINE

VOLUME 38 MAY, 1953 NUMBER 5

THE USE OF ACTH AND CORTISONE IN THE TREATMENT AND IN THE DIFFERENTIAL DIAGNOSIS OF MALIGNANT EXOPHTHALMOS: A PRELIMINARY REPORT*

By LAURANCE W. KINSELL, M.D., F.A.C.P., JOHN W. PARTRIDGE, M.D.,† and NADINE FOREMAN, M.D., *Oakland, California*

THE present report comprises the findings in nine patients who have been studied during the past two years, all of whom presented the complaint of exophthalmos of severe or moderately severe degree, in association with obvious or probable thyroid dysfunction.

CLINICAL OBSERVATIONS

Patient G. T. was referred through the kindness of Dr. Gale Whiting and Dr. Owen Dickson. Three months prior to admission she had had a thyroidectomy for a toxic goiter in association with exophthalmos of moderate degree. Following surgery the exophthalmos became progressively worse and, despite the administration of desiccated thyroid, reached a magnitude sufficient to endanger both eyes seriously. Decompression surgery was contemplated.

Initial treatment consisted of the administration of 40 mg. of ACTH per 24 hours by continuous slow intravenous drip, plus cortisone acetate,

* Received for publication March 3, 1953.
This material was presented in part at the Graduate Assembly, sponsored jointly by the Alameda Contra Costa County Medical Association and the Institute for Metabolic Research, February 5, 1953.
From the Institute for Metabolic Research, Highland Alameda County Hospital, Oakland, California.
† Schering Research Fellow in Endocrinology, 1950–52.
Grateful acknowledgment is made to the Armour Laboratories for supplies of ACTHAR Gel, to Merck & Company for supplies of Cortone and Hydrocortone used in some of these studies, and to the Schering Corporation for ethinyl estradiol (Estinyl), and testosterone propionate (Oreton).

Copyright, 1953, by The American College of Physicians

100 mg. per day, administered orally (25 mg. every six hours). On this regimen her exophthalmos, which immediately prior to therapy measured 21 mm. in the right eye and 22 mm. in the left eye (Hertel), had decreased to O.D. 19, O.S. 18, at the end of 24 hours. This improvement continued, and by the fourth day no clinical exophthalmos was present (O.D. 16 mm., O.S. 17 mm.), although major abnormality of function of the extra-ocular muscles persisted. Diplopia was significantly improved.

When the patient was placed on 15 mg. of intramuscular ACTH every 12 hours, and 25 mg. of oral cortisone every six hours, some exacerbation of the exophthalmos occurred. Dosage was accordingly increased, and the patient was discharged from the hospital at the end of 28 days on a dosage of 20 mg. of ACTH gel intramuscularly every 12 hours. She also received testosterone propionate, 25 mg. daily, and 37.5 mg. of cortisone acetate every six hours.

Over a period of three months, during which time the patient developed rather major Cushingoid manifestations, at times in association with considerable emotional instability, the dosage of ACTH and cortisone was progressively diminished, as was the dosage of testosterone. Acne and hirsutism became a major problem. Administration of estrogen, as ethinyl estradiol, in a dosage of 0.1 mg. daily, appeared to modify favorably both the hirsutism and the acne, and may have lessened the emotional instability. At the end of five months of treatment, ACTH was discontinued and the patient was maintained on oral cortisone alone. Eight months later local cortisone (and later hydrocortisone acetate) was instilled into the eyes at hourly intervals throughout the day. Shortly thereafter all systemic therapy was stopped and local hydrocortisone continued. At present the patient is maintained on local medication, every two hours during the day, and has no residuum of her disease or of her treatment except for some moderate abnormality of function of the extraocular muscles, which presumably is referable to permanent replacement of muscle tissue by scar tissue.

Eight other patients with exophthalmos of varying degrees of severity have been treated in a fashion similar to the above. Without exception, significant decrease in exophthalmos has occurred within 48 hours of commencement of therapy and has been maintained with continued therapy. In two patients, systemic therapy was of necessity discontinued, in one instance because of the development of severe psychotic manifestations, which disappeared when systemic treatment was stopped, and in the other because of the development of perforation of a peptic ulcer. This latter patient made a rapid and uneventful convalescence from her perforation, and was discharged from the hospital five days after surgery. (Systemic ACTH and cortisone were discontinued three days after surgery.) In both of these patients, fair control of the exophthalmos was maintained with local instillation of hydrocortisone acetate at frequent intervals. A patient, H. V., seen recently, with a definite ulcer history and with other findings incom-

patible with systemic ACTH and cortisone therapy, was placed immediately on local hydrocortisone acetate, and up to the present time has experienced symptomatic improvement in the manifestations of the exophthalmos.

Patient E. S., a boy of 11, was referred for treatment of severe unilateral "malignant exophthalmos," which had developed rapidly over a period of approximately one month. The serum protein bound iodine was alleged to be 1.2 mcg. per cent. On the basis of this finding he had received rather intensive treatment with desiccated thyroid, without benefit. Roentgenograms revealed no findings which were definitely diagnostic of tumor. It was our impression, however, that tumor was a greater probability than thyrotropic exophthalmos. It was therefore agreed that intensive ACTH therapy would be limited to four days, and that if no improvement occurred, exploratory surgery would ensue. No change in exophthalmos had occurred by the end of the fourth day.

Exploration revealed a rapidly growing malignant tumor in the posterior orbit, histologically a "primitive glioma," which up to the present time has responded to radiation therapy.

Discussion

The precise mechanism of "thyrotropic" exophthalmos is still by no means clear, but it seems reasonably well established that the disease is referable either to an effect of thyrotropin per se, or of some material of pituitary origin which is intimately associated with thyrotropin. The local pathology consists of the retrobulbar accumulation of a tissue in which mononuclear cells, mast cells and fat may be prominent, and of mononuclear cell infiltration and fibroplastic proliferation in the extra-ocular muscles.[1] Ideal treatment, therefore, would consist of the administration of an agent which would both inhibit the excess thyrotropin and cause a "lysis" of the abnormal tissue in the extra-ocular muscles and behind the eye.

On the basis of reports by Hill et al. and by Wolfson and his associates,[2] it seems probable that ACTH and cortisone do exert some inhibiting effect upon thyrotropin, although this concept has not been fully accepted or confirmed.

The work here reported was undertaken because of the known "lytic effects" of adrenal steroids upon mononuclear cells, and with the working hypothesis that sufficient amounts of corticotropin and cortisone and related steroids *would* inhibit thyrotropin production. On the basis of our observations thus far, it appears that one or both of these effects do occur, and that intensive corticotropin-cortisone therapy, at least in many instances, will eliminate the need for decompression surgery of the orbit in patients with exophthalmos of sufficiently severe degree to endanger the survival of one or both eyes.

It appears advisable to administer ACTH (20 to 40 units per liter of solution containing 5 per cent dextrose with 0.2 per cent KCl) by continuous intravenous drip (rate, 100 c.c. per hour) throughout the first three days

of treatment, together with 200 to 600 mg. of cortisone by the oral or intramuscular route, daily. Thereafter, ACTH gel may be administered at 12 hourly intervals, in a dosage of 20 to 80 units per day. Both ACTH and cortisone are decreased as rapidly as the clinical status of the patient permits. Very prolonged administration may be required in some patients.

In this small group, the occurrence of a rather high incidence of untoward effects emphasizes the need for the use of all measures, dietary and hormonal, known to modify such effects favorably.[3] Estrogen should probably be administered routinely in all female patients, since it not only "neutralizes" some of the catabolic effects of ACTH-cortisone, but also has been reported to have some "antithyrotropic effect" and possibly some effect on the abnormal orbital tissue.[4]

Reports of therapeutic effectiveness of ACTH and cortisone in malignant exophthalmos have been controversial.[2, 5] We believe that in many instances inadequate therapeutic response has been referable to inadequate dosage.

Summary

On the basis of nearly two years' observation in a small group of patients, it appears that the administration of systemic ACTH and of local and systemic cortisone and hydrocortisone will favorably modify "thyrotropic exophthalmos." This effect may be produced in a dual fashion, i.e., on the basis of "lysis" of the abnormal tissue deposited within the extra-ocular muscles and behind the eye, as well as on the basis of inhibition of thyrotropin production. On the basis of experience with one patient, the procedure may also have value in the differential diagnosis between thyrotropic exophthalmos and exophthalmos resulting from retrobulbar tumor.

Addendum

Since the submission of this paper, one additional patient, C. S. (referred through the courtesy of Dr. Ralph Teall), has been treated in the manner outlined above. She differed from the other patients in the series in that she is alleged always to have had "prominent eyes," i.e. even prior to the onset of her hyperthyroidism. Following thyroid surgery in January, 1953, she had increasing diplopia. With administration of intensive ACTH and cortisone, the diplopia allegedly improved, retrobulbar resistance diminished, but there was relatively slight improvement in eye measurements. In addition, on very large dosage of ACTH and cortisone, her eosinophil count did not fall below 50 per cubic millimeter and her 17-ketosteroids rose much less than one would expect with such dosage. The long-term clinical course of this patient will be reported later. It would appear that she is resistant to both corticotropin and cortisone in a biochemical and a clinical sense.

BIBLIOGRAPHY

1. Naffziger, H. C.: Progressive exophthalmos following thyroidectomy; its pathology and treatment, Ann. Surg. **94**: 582, 1932.
2. (a) Hill, S. R., Jr., Reiss, R. S., Forsham, P. H., and Thorn, G. W.: The effect of adrenocorticotrophin and cortisone on thyroid function: thyroid-adrenocortical interrelationships, J. Clin. Endocrinol. **10**: 1375, 1950.
   (b) Wolfson, W. Q., Beierwaltes, W. H., Robinson, W. D., Duff, I. F., Jones, J. R., Knerpp, C. T., Siemienski, J. S., and Eya, M.: Corticogenic hypothyroidism: its

incidence, clinical significance and management during prolonged treatment with ACTH or cortisone, Proceedings Second Clinical ACTH Conference, Vol. 2, J. R. Mote, Editor, 1951, The Blakiston Company, Philadelphia.

3. Kinsell, L. W., Partridge, J. W., Boling, L., and Margen, S.: Dietary modification of the metabolic and clinical effects of ACTH and cortisone, Ann. Int. Med. **37**: 921, 1952.
4. (a) François, J.: Estrogen therapy in Graves' disease, Bull. Soc. belge d'opht. **97**: 194, 1951.
   (b) Smelser, G. K., and Ozanics, V.: Relation of steroid hormones to the development of experimental exophthalmos, Am. J. Ophth. **34**: 87, 1951.
5. (a) Salassa, R. M.: Effects of cortisone and ACTH in certain endocrine conditions, Proc. Staff Meet., Mayo Clin. **25**: 497, 1950.
   (b) Woods, A. C.: Present status of ACTH and cortisone in clinical ophthalmology, Am. J. Ophth. **34**: 945, 1951.
   (c) Fitzgerald, J. R., Bellows, J. G., Donegan, J. M., Gamble, R. C., Krause, A. C., Mann, W. A., Pearlman, M. D., and Zekman, T. N.: Early clinical results of ACTH and cortisone treatment of ocular disease, Arch. Ophth. **45**: 320, 1951.
   (d) Chandler, G. N., and Hertfall, S. J.: Cortisone and ACTH in exophthalmic ophthalmoplegia, Lancet **1**: 847, 1952.

THE HYPERVENTILATION SYNDROME*

By BERNARD I. LEWIS, M.D., F.R.C.P.(C)., F.A.C.P., *Iowa City, Iowa*

THE hyperventilation syndrome is generally considered an acute, transitory episode characterized by gross hyperpnea and culminating in frank tetany. Because of its presumed low incidence and clinical insignificance, it has received scanty attention in the current literature and is virtually ignored by the standard medical texts. Recent observations at the University Hospitals of the State University of Iowa College of Medicine suggest that, contrary to prevalent opinion, hyperventilation syndromes occur frequently; pursue a chronic, fluctuating course more often than one featuring brief, explosive attacks with asymptomatic intervals; present variegated, atypical clinical pictures, commonly attended by significant incapacitation; and may arise from either organic or psychogenic mechanisms, or combinations of both.

SYMPTOMATOLOGY

The spectacular acute forms of this syndrome are easily recognized. When chronic patterns develop, various symptoms infrequently linked with the hyperventilation complex become increasingly prominent. In consequence, diagnosis is proportionately more difficult. To illustrate the widespread effects of prolonged overbreathing, a convenient grouping of the more common manifestations follows:

1. Central neurovascular: faintness, dizziness, unsteadiness, impairment of concentration and memory, feelings of unreality and, infrequently, complete loss of consciousness.
2. Peripheral neurovascular: numbness, tingling and coldness of the distal extremities, especially the hands, and often involving the face and perioral regions.
3. Muscular: variable, usually diffuse, muscular spasm and myalgia, coarse tremors, twitching movements and, uncommonly, carpopedal spasm with generalized tetany.
4. Respiratory: shortness of breath, tightness in or about the chest and, less impressive but equally significant, sighing respirations and excessive yawning.
5. Cardiac: palpitations, tachycardia, "skipped beats" and atypical chest pain. The chest pain is usually described as momentary, sharp twinges about or lateral to the nipple, or as a more persistent, dull, aching pressure over the lower anterior thorax.

* Presented in part at the Midwest Regional Meeting of the American College of Physicians, Chicago, Illinois, November 22, 1952. Received for publication December 12, 1952.
From the Department of Internal Medicine, College of Medicine, State University of Iowa, Iowa City, Iowa.

6. Gastrointestinal: marked mouth dryness, dysphagia (often suggestive of globus hystericus) and distressing abdominal bloating, belching and flatulence.

7. Psychic: variable degrees of overt anxiety, tension and apprehension except in certain hysterical subjects, who display an inappropriate pseudo-calmness.

8. General: easy fatigability, diffuse weakness, insomnia and chronic exhaustion.

Pathophysiology

The hyperventilation syndrome is widely held to have a psychogenic etiology. This is not always the case. Identical patterns have been observed secondary to central nervous system disorders such as encephalitis and drug encephalopathies (e.g., salicylate intoxication).[1] Acute attacks have occurred in healthy young men consequent to respiratory dysfunction during high altitude flying; they may be precipitated, as well, in stable individuals as part of an intense emotional reaction (e.g., secondary to extreme pain, panic or anger).[2] Organic disease in remote areas of the body has initiated hyperventilation mechanisms by reflex sensory stimulation.[3] I suspect, moreover, that psychogenic hyperventilation syndromes are superimposed upon organic illnesses far more frequently than is now recognized. The coexistence of these processes not only provides diagnostic and therapeutic problems but also results in mutually adverse effects.

Despite the variable nature of the causal process, the primary link in the pathophysiologic chain is hyperventilation. This becomes clinically important when, by virtue of an increase in the rate and/or depth of respiration, sufficient CO_2 is blown off to lower significantly the arterial CO_2 content and produce an alkalotic state. That alkalosis can be easily and rapidly induced is evidenced by two observations: (1) A single deep respiration will decrease the arterial CO_2 concentration by 5 to 7 vols. per cent and the CO_2 tension by 7 to 16 mm. of mercury.[4] (2) Most of the CO_2 reduction in sustained overbreathing is accomplished during the first 30 to 60 seconds.[2] With the advent of respiratory alkalosis certain biochemical, neurovascular and neuromuscular changes follow which are fundamental to the multiple features of the hyperventilation syndrome.

A variable degree of slowing in the frequency of the brain waves occurs in the central nervous system. This is closely correlated with alterations in the level of consciousness. When the mean electroencephalographic frequency falls below 5 cycles per second, conscious awareness is markedly reduced.[2] These changes are importantly related to the acapnia and, in minor degree, to a relative cerebral anoxia. The relative anoxia results from a reduced cerebral blood flow and decreased oxyhemoglobin dissociation, which are effected initially by the lowered arterial CO_2 content.[5]

Several factors accentuate the electroencephalographic slowing and the parallel impairment of consciousness. These are (1) the rapidity of fall in

arterial CO_2 content, (2) a low blood sugar, (3) a low oxygen tension in the inspired air, and (4) the erect posture.[2] When factors opposing these are operative, the central nervous system changes are less marked and hyperventilation tends to persist. With prolonged hyperventilation, frank tetany is likely to develop. This occurs infrequently, as consciousness is usually reduced sufficiently to stop the overbreathing and thus prevent the tetany. In a sense, then, the changes in the level of awareness, variously described as faintness, dizziness, blackout spells and the like, serve a protective function. I believe that many predisposed subjects, while thus inhibiting overt tetany, tend to develop a chronic psychophysiologic state characterized by fluctuating hyperpnea, borderline CO_2 deficit and variable impairment of consciousness. Diverse symptomatic patterns accompany these basic changes, and the chronic course is punctuated by recurring acute episodes. As the respiratory component is often camouflaged by more prominent features, the resultant clinical picture is particularly confusing.

The peripheral and perioral paresthesias are not of central origin and do not correlate with the electroencephalographic changes.[2] They result from local neurovascular changes induced by the lowered CO_2 levels, with its secondary peripheral vasoconstriction and relative anoxia. The muscular manifestations, including tetany, probably arise from similar alterations affecting the myoneural junction. The blood calcium level does not play a vital rôle in these changes. For reasons yet unclear, these peripheral features are occasionally asymmetrical and may even be unilateral.

The respiratory alterations, from frequent sighing and yawning to gross hyperpnea, are quite evident to the examiner. The patient, paradoxically, is often unaware of disordered breathing, even though breathlessness, difficulty in obtaining a full, satisfying breath, or a sense of restrictive pressure about the lower chest is a frequent secondary complaint. These subjects tend to demonstrate a peculiar, heaving type of respiration involving the upper thorax that calls into play their accessory respiratory muscles. This may persist during apparently quiet breathing, and fluoroscopic studies have revealed the presence of a depressed, relatively immobile diaphragm.[6]

Cardiac symptoms are very common and are often the presenting complaint. The circulatory changes accompanying this syndrome are not too well understood, however, and require further investigation. It is known that the vasomotor centers function efficiently only at adequate CO_2 tensions. Reduction in the arterial CO_2 content causes direct inhibition of the vasomotor centers, which is reinforced reflexly through the aortic and carotid chemoreceptors. This induces splanchnic vasodilatation and a considerable drop in blood pressure. Peripherally, however, the lowered CO_2 content exerts a direct constrictor effect upon the arteriolar wall. Thus, circulatory changes are dependent upon the net result of these opposing forces.[5] Definite, consistent effects have not yet been demonstrated, although a reduction in venous return, with consequent decreased cardiac output, has been reported.[7] This may induce tachycardia reflexly and accentuate the peripheral

vasoconstriction. Electrocardiographic studies have confirmed the production of extrasystoles and significant alterations in the S-T segments and T waves.[8] The precordial stabbing pains have been correlated with the onset of arrhythmias[9] and with diaphragmatic spasm.[10] At other times they appear secondary to gaseous distention of the stomach with pressure on the diaphragm. The prolonged aching chest pain may be caused by persistent spasm of the intercostal muscles, and such areas of spastic myalgia have been detected clinically.

Gastrointestinal complaints are also common but are seldom as prominent as those referable to the cardiovascular system. Marked oral dryness is usually present, though it may not be a spontaneous complaint. It is related, in part, to the overbreathing and drying of the mucous membranes. Whether some degree of hyposalivation is effected by alterations in parasympathetic activity is not clear. Bloating, belching and flatulence comprise a characteristic symptomatic triad and result from the aerophagia that commonly attends this syndrome. Percussion over the left upper quadrant of the abdomen generally elicits an exaggerated tympanitic note. The recent report of a so-called "splenic flexure syndrome," [11] based on the trapping of gas in this sharply angulated flexure, may well be another variation on the hyperventilatory and aerophagic theme.

Emotional manifestations of varying nature and degree are almost always evident. Premorbid psychic patterns are accentuated and new emotional responses tend to appear in reaction to the alarming symptoms. Anxiety, tension and apprehension are generally obvious, but may be thinly concealed in certain hysterical subjects by an inappropriate façade of pseudocalmness. Affective reactions are most prominent during or at the termination of acute episodes, whether spontaneous or deliberately produced by the physician. This characteristic release of emotionally charged material provides the patient with symptomatic relief and usually supplies the physician with pertinent information he might otherwise not obtain.

The complaints of generalized weakness, ease of fatigue and exhaustion are easily understandable when the effort of chronic hyperpnea and the energy consumed by the psychic factors are taken into account. Patients with coexistent organic disease typically attribute all their disturbing symptoms to the structural process, which aggravates and exaggerates their total disorder. Although precise evaluation of such distorted symptomatic patterns is exceedingly difficult, unfortunately, these are the illnesses for which an accurate diagnosis and requisite therapy are particularly important.

Several case histories will be presented in brief to illustrate some of the diverse clinical syndromes that may be encountered.

Case Reports

Case 1. A 50 year old unmarried nurse entered hospital with an exacerbation of her chronic intrinsic asthma. She improved rapidly on symptomatic treatment and, after one week in hospital, was told she would be discharged the following day.

That evening she complained of tightness in her chest and received 3 minims of epinephrine subcutaneously. Within 10 minutes she developed an acute episode characterized by generalized muscular twitching, clonic movements of the extremities, bloating, belching, tachycardia, dyspnea and disorientation. The recorded differential diagnosis of the resident who saw her consisted of hypertensive encephalopathy, coronary thrombosis or a cerebrovascular accident. She received morphine hypodermically, after which the manifestations slowly subsided. The following morning she was weak and tired but otherwise asymptomatic. While discussing the episode with her she spontaneously staged a repeat performance which was typical of the hyperventilation syndrome. This was quickly resolved by having her rebreathe from a paper bag.

Case 2. A 32 year old housewife was admitted to hospital with a three months' history of polyarthritis, tachycardia, chest pain, shortness of breath, headache and "blackout spells." The referring physician's diagnosis was acute rheumatic fever. Investigation in hospital revealed the supposed polyarthritis to be a diffuse, spastic myalgia without evidence of joint involvement. The only cardiac finding was a labile tachycardia. Her chest pain consisted of transitory, non-radiating precordial twinges located lateral to the nipple line. Her shortness of breath suggested hyperpnea rather than dyspnea, and was described as a difficulty in obtaining a deep, satisfying breath. Her headache was a typical tension cephalalgia, and the "blackout spells" were periods of lightheadedness associated with hyperpnea. Direct inquiry elicited the presence of paresthesias of the hands and feet coincidental with these acute spells. She was obviously quite tense and apprehensive but denied any specific worries. She was requested to hyperventilate, and after two and one-half minutes of overbreathing developed a characteristic attack with the reproduction of all her symptoms. This episode was rapidly terminated by having her rebreathe in a paper bag.

Case 3. A 25 year old unmarried woman was admitted to hospital with a three weeks' history of diffuse musculoskeletal pain and stiffness, palpitations and shortness of breath. The referring physician had considered as diagnostic possibilities poliomyelitis or acute rheumatic fever. The patient was a known diabetic of 18 years' duration who had been under the constant supervision of the Department of Pediatrics. Detailed information on her past medical history was thus available. Intensive investigation in hospital revealed no evidence of poliomyelitis, rheumatic fever or an arthritic process, but did demonstrate widespread muscular spasticity, moderately uncontrolled diabetes and a peculiar indifference to her apparent illness. The atypical manifestations and her inappropriate emotional state raised the question of a psychogenic disorder, and survey of her past records confirmed such a predisposition. Careful inquiry disclosed the presence of recurring, acute episodes of muscular tightness and twitching, associated with peripheral paresthesias, beneath her diffuse spastic myalgia. The patient indulged in frequent sighing respirations and appeared moderately breathless most of the time. A subacute, or early chronic, hyperventilation syndrome was suspected and the patient was requested to overbreathe. A typical exacerbation of her symptoms, with a mild degree of tetany, was precipitated in approximately three minutes. The paper bag technic quickly ended the attack.

Case 4. A 47 year old housewife entered hospital for evaluation of her cardiac status. She gave a seven year history of coronary heart disease with severe angina pectoris, and one period of hospitalization elsewhere for an acute myocardial infarction. The patient had consumed tremendous quantities of nitroglycerin and papaverine through the years, and insisted she was now completely dependent upon an oxygen inhalation apparatus in her home, with supplementary narcotics for the more severe attacks. In view of certain atypical features in her history, the relative lack of physical findings and normal electrocardiographic studies, a search was made for other factors that might be operative. Review of her records from the other hospital

provided no evidence to substantiate the previous diagnosis of myocardial infarction. Careful inquiry revealed that her acute episodes often occurred at rest and those associated with exertion commonly occurred after rather than during a period of effort. She was found to have atypical, knife-like chest pain; was noted to be hyperpneic rather than dyspneic, and was constantly and apprehensively aware of the heavy pounding of her heart, even though tachycardia was only occasionally present. Moreover, in conjunction with her "heart attacks," she experienced marked bloating, belching and flatulence and uncomfortable tightness, numbness and tingling about the mouth and left hand. She denied any unusual sensations or changes in the right hand. On examination, diffuse hyperhidrosis, generalized hyperreflexia, frequent sighing respirations with recurring, transient hyperpnea and marked aerophagia were evident. Voluntary overbreathing for two and one-half minutes induced one of her characteristic episodes, which was quickly abated with the paper bag method.

The reproduction and dramatic termination of a typical acute attack in each of these patients provoked a marked emotional reaction and the disclosure of important data pertinent to the related, disturbing life situation. This experience seemed to afford them significant symptomatic relief which was sustained and augmented by suitable explanation and reassurance. The first patient has had but one minor recurrence in 19 months, which she herself quickly controlled with a paper bag. The second patient is known to have remained asymptomatic for at least six months, and has not been rechecked since that time. The third patient has been symptom-free for 13 months, with her previously labile diabetes now well controlled. The morning after her induced attack, the fourth patient announced that she had slept through the night for the first time in seven years and felt like a "new woman." This remarkable improvement has been maintained during the five months since her discharge from hospital.

Organic hyperventilation syndromes do not appear to follow this type of chronic, fluctuating course. They tend rather to feature more circumscribed, acute episodes, which often terminate in frank tetany. The following cases exemplify this pattern.

Case 5. An 18 year old construction worker was admitted to hospital with a bizarre illness of two months' duration. In its early stages this illness had featured atypical abdominal pain for which an appendectomy was performed. As far as could be ascertained, a normal appendix and a grossly normal abdomen were found. The postoperative course was protracted and characterized by hyperthermia, anhidrosis, recurring episodes of orthostatic hypotension and syncope, causalgia-like pain over both feet, anorexia, a 30 pound weight loss, an atonic colon, marked weakness, unusual somnolence and distinct personality changes. While on the ward he exhibited several acute febrile episodes, with pyrexia to 103°, which were associated with explosive attacks of hyperventilation tetany. These were of relatively brief duration and were terminated by the ward physician with 10 mg. of morphine on several occasions. Unfortunately, no attempt was made to utilize the paper bag technic. These episodes subsided coincidently with the patient's general improvement on symptomatic therapy. At the time of discharge the only residuum was moderate orthostatic hypotension, fairly well controlled by leg binders and 40 mg. of Paredrine four times daily. Intensive investigation in hospital failed to provide a definite diagnosis but did reveal clinical evidence of diffuse autonomic dysfunction suggesting a widespread central nervous system process, with particular involvement of the hypothalamic centers.

Whether the etiologic mechanism was of an infectious nature or on a nutritional basis, or otherwise, remains unclear. It did appear, however, that these hyperventilation episodes were organically engendered and but one reflection of a diffuse neurologic disease.

Case 6. A 28 year old widow entered hospital with a six months' history of progressive muscular pain and weakness, particularly of the upper extremities, general malaise, anorexia, mild weight loss, swelling of the eyelids and an erythematous rash over the face and upper arms. The clinical impression favored a collagen vascular disease and, subsequent to extensive laboratory procedures, including muscle biopsy, a diagnosis of dermatomyositis was confirmed. Clinical neurologic examination was negative but an electroencephalogram was reported as abnormal, with an unexplained focus over the left temporal region. The patient was placed on treatment with ACTH and, subsequently, cortisone, but after preliminary improvement she followed a steady downward course and died. During her stay in hospital she manifested a number of acute hyperventilation attacks associated with peripheral paresthesias and muscle spasm. These were consistently and quickly controlled by having her rebreathe from a paper bag. Although final proof is lacking, it is probable that these episodes were organically rather than psychogenically precipitated.

Discussion

These representative cases portray some of the guises under which the hyperventilation syndrome may appear, and demonstrate the difficulty of delineating a characteristic clinical picture. Acute classic attacks are easily detected. The more frequent, chronic patterns, which masquerade behind symptoms referable to localized organs and systems, are less often recognized. The effects of chronic hyperventilation and impaired consciousness tend to complicate matters by further distorting, and rendering less valid, the perplexing stories offered by these patients. Consequently the physician must have a high index of suspicion and peer behind the scenes, if he is to ferret out the important diagnostic clues.

The chief complaints generally suggest a cardiovascular, neurologic or musculoskeletal process, although the occasional pseudocholecystic disease pattern is encountered. Careful inquiry will usually reveal the atypical nature and course of these presenting complaints, and at the same time disclose features indicative of a hyperventilation mechanism. Peripheral and perioral paresthesias are the most consistent symptoms, and disordered breathing, from simple sighing respirations to frank hyperpnea, the most common sign. Patients mention the paresthesias infrequently, and then only casually, and are characteristically oblivious to their disordered breathing. In contrast to the organic processes with which they may be confused, exacerbations of the hyperventilation syndrome tend to occur at rest, particularly at night or in the morning when the subject is just falling asleep or awakening. Some patients do correlate their complaints with exertion, but their attacks are generally found to arise after effort, not during it. Patients with an organic hyperpnea tend to manifest recurring, acute hyperventilation attacks, whereas subjects with organic disease and secondary psychogenic hyperventilation generally develop the more chronic course.

Hyperventilation syndromes have been observed in conjunction with many organic states. Subjects with coronary, hypertensive and rheumatic heart disease, pulmonary emphysema, bronchial asthma and the Stokes-Adams syndrome are reported to be especially predisposed; and unexplained breathlessness in digitalized, compensated cardiacs has been frequently related to this mechanism.[8]

The true incidence of symptomatic hyperventilation is unknown but is likely much greater than is now realized. I strongly suspect that the pathophysiologic effects of sustained overbreathing underlie some and, on occasion, all manifestations of many patients with so-called neurocirculatory asthenia, cardiac neurosis, anxiety reaction, functional dyspepsia, atypical fibromyositis, chronic nervous exhaustion and the like. Further investigation will confirm or deny the validity of this statement. Be that as it may, valuable diagnostic data will be derived from an evaluation of the effects of hyperventilation in all patients with atypical cardiorespiratory, neurovascular, neuromuscular and gastrointestinal syndromes.

Therapy

A detailed discussion of therapeutic measures is beyond the scope of this presentation. Nevertheless, certain working principles merit brief comment. Concurrent organic disease obviously demands specific attention. Similarly, psychotherapy is the basic requisite for the psychogenic manifestations. Few patients with this disorder are seen initially by a psychiatrist. In general, they are the responsibility of the nonpsychiatric physician, who must evaluate the problem and identify the underlying processes. When a hyperventilation mechanism is suspected, the successful reproduction of the symptom-complex with induced overbreathing is of cardinal importance. To the patient this acute precipitation of his attack is both alarming and impressive, and its immediate termination with the paper bag technic is proportionately reassuring. The accompanying emotional catharsis provides him with considerable symptomatic relief and, at the same time, furnishes the physician with significant insight into the related personal difficulties. This experience greatly strengthens the all-important doctor-patient relationship.[12] Furthermore, it demonstrates to the patient that his complaints are real, not imaginary, yet serves to convince him of their primary emotional basis. Suitable explanation and reassurance will enhance his understanding of the benign nature of these symptoms and dissipate his fears of serious physical disease. This may be all that is necessary to enable the patient to consider and contend with his fundamental problems. In any event, the stage is now set for the formulation and institution of rational therapy directed toward a realistic goal.

Summary and Conclusions

Contrary to prevalent opinion, this study revealed that hyperventilation syndromes:

1. Occurred relatively frequently.
2. Pursued a chronic, fluctuating course more often than one featuring brief, explosive attacks with asymptomatic intervals.
3. Presented atypical clinical pictures, with the respiratory component generally masked by prominent symptoms referable elsewhere.
4. Arose from either organic or psychogenic mechanisms, or combinations of both.

Regardless of the nature of the basic mechanism, sustained overbreathing is the primary link in this pathophysiologic chain of events. Widespread biochemical, neurovascular and neuromuscular changes are thus induced. The resultant symptoms and signs suggest neurologic, musculoskeletal, respiratory, cardiovascular, gastrointestinal and/or psychiatric disorders.

The case summaries illustrate some of the atypical clinical pictures and the variable guises under which the hyperventilation syndrome appeared. Peripheral paresthesias were the most consistent symptoms, and disordered breathing was the most common sign. As these were seldom prominent features, a high index of suspicion was required to detect the important diagnostic clues.

An accurate diagnosis is doubly important, and proportionately difficult, when organic disease and psychogenic hyperventilation coexist; this combination probably occurs much more frequently than is now recognized. The pathophysiologic effects of chronic hyperventilation may underlie many of the manifestations of neurocirculatory asthenia, "functional" cardiac and gastrointestinal states, atypical fibromyositis and other myalgias, anxiety-tension reactions and chronic nervous exhaustion.

Voluntary overbreathing will precipitate a typical, acute attack, and rebreathing from a paper bag will terminate it. These combined procedures have both diagnostic and therapeutic value inasmuch as they:

1. Can reproduce the patient's alarming symptoms and dramatically abolish them.
2. Demonstrate the reality and at the same time the psychophysiologic basis of these symptoms.
3. Provide the patient with immediate symptomatic relief and a simple technic for terminating future attacks.
4. Furnish the physician with additional insight into the related personal difficulties.
5. Strengthen the all-important doctor-patient relationship.
6. Set the stage for a rational and realistic therapeutic program.

BIBLIOGRAPHY

1. Ryder, H. W., Shaver, M., and Ferris, E. B.: Salicylism accompanied by respiratory alkalosis and toxic encephalopathy, New England J. Med. **232**: 617, 1945.
2. Engel, G. L., Ferris, E. B., and Logan, M.: Hyperventilation: analysis of clinical symptomatology, Ann. Int. Med. **27**: 683, 1947.

3. Stead, E. A., Jr., and Warren, J. V.: Clinical significance of hyperventilation, Am. J. M. Sc. **206**: 183, 1943.
4. Ferris, E. B., Stevens, C. D., Webb, J. P., and Engel, G. L.: Voluntary breathholding. III. The relation of the maximum time of breathholding to the oxygen and carbon dioxide tensions of arterial blood, J. Clin. Investigation **25**: 734, 1946.
5. Wright, Samson: Applied physiology, 1952, Oxford University Press, New York.
6. Willard, H. N., Swan, R. C., Jr., and Wolfe, G. A., Jr.: Life situations, emotions and dyspnea, *in* Life stress and bodily disease, 1950, Williams & Wilkins, Baltimore, p. 583.
7. Short, J. J.: The hyperventilation syndrome, Postgrad. Med. **7**: 85, 1950.
8. Thompson, W. P.: The electrocardiogram in the hyperventilation syndrome, Am. Heart J. **25**: 372, 1943.
9. Friedman, M.: Studies concerning the etiology of the pathogenesis of neurocirculatory asthenia. III. The cardiovascular manifestations of neurocirculatory asthenia, Am. Heart J. **30**: 438, 1945.
10. Wolf, S.: Sustained contraction of the diaphragm; the mechanism of a common type of dyspnea and precordial pain (Abstract), J. Clin. Investigation **26**: 1201, 1947.
11. Machella, T. E., Dworken, H. J., and Biel, F. J.: Observations on the splenic flexure syndrome, Ann. Int. Med. **37**: 543, 1952.
12. Lewis, B. I.: Psychosomatic disorders and the nonpsychiatrist, J. A. M. A. **150**: 776, 1952.

REMISSION OF INTRACTABLE ALLERGIC SYMPTOMS BY ACUTE INTERCURRENT INFECTIONS *

By Joseph H. Fries, M.D., F.A.C.P., *Brooklyn, N. Y.*, and Stanford Borne, M.D., *Valley Stream, N. Y.*

It is common knowledge that upper respiratory and other bacterial infections may have an adverse effect on the course of chronic allergic symptomatology. This effect is a recurrent theme in the medical literature.[1-4] Less well annotated is the temporary clearance of intractable allergic symptoms which may result from an acute intercurrent infection.[5-7]

Thirty-two atopic children, while under our observation, showed a temporary remission of their allergic symptoms following a viral or bacterial infection. An integration of our cases with some of those previously reported in the literature emphasizes the veracity of this phenomenon.

Clinical Features

During the past several years one of us (J. H. F.) has observed 16 patients in whom an acute infection could be said to have caused a temporary remission of severe, persisting allergic symptoms (asthma, atopic dermatitis, allergic rhinitis). Eleven subjects had measles, two had pneumonia, one had scarlet fever, and two had upper respiratory infections with sore throats. Observed by both authors were 16 subjects with Kaposi's varicelliform eruption due to vaccinia virus (table 1). With the exception of these patients with Kaposi's varicelliform eruption, whose course was followed only during their hospital stay for the acute illness (and who therefore are not included in table 1), all were observed personally for a period of time varying from months to several years before and after the intercurrent infection.

Every patient described had been suffering with severe allergic symptoms (such as daily asthma, constant perennial rhinitis, or persistent, marked eczematosis) for a prolonged period of time up to the development of the intercurrent infection.

In several instances modification of the allergic status was dramatic. In these the remission period was sufficiently long as to delude the patient (or the parents) into a feeling of complete recovery. One subject (J. G.) with gastrointestinal symptoms (celiac syndrome, probably of allergic origin) had a persisting remission. There has been no relapse for five years.

It will be noted that five children suffered from two coexisting manifestations of allergy. In every instance, both allergic processes were altered

* Received for publication December 2, 1952.
From the Allergy Department, Lutheran Hospital, Brooklyn, N. Y.

TABLE I
Analysis of Cases

Case No.	Name	Age (yrs.)	Sex	Allergic Symptoms			Intercurrent Illness	Remission Period	Comment
				Type	Duration	Severity			
1	S. A.	7	F	Asthma	5 mos.	Slight to severe wheezing several times a week	Measles	12 mos.	Severe measles.
2	E. B.	1½	M	Asthma	1 yr.	Attacks almost daily	Measles	2 weeks	Concomitant clearance and return of asthma and dermatitis.
				Atopic dermatitis	1 yr.	*Eczema++++			
3	J. B.	2½	M	Asthma	2 yrs.	3 to 4 attacks a month	Measles	5 mos.	Concomitant clearance and return. Subsequent appendectomy at 10 yrs. of age relieved asthma for 6 months; no effect on residual eczema.
				Atopic dermatitis	2 yrs.	*Eczema++++			
4	J. K.	2	M	Asthma	1½ yrs.	Severe	Measles	6 weeks	Almost daily asthma attacks for 36 days before measles onset.
5	P. L.	4	F	Asthma	4 yrs.	Severe	Measles	2½ weeks	Daily asthma with frequent "status asthmaticus" for 6 months preceding measles.
6	S. P.	7	M	Allergic rhinitis	2½ yrs.	Constant nasal blockage	Measles	6 weeks	Longest "free" period in an illness of 2½ years' duration.
7	P. S.	6	F	Asthma	5 yrs.	Moderate	Measles	1 mo.	Moderately severe attacks every 5 to 7 days for several months preceding measles.
8	J. G.	1	F	Atopic dermatitis	8 mos.	*Eczema+++	Measles	3 weeks	At 8 years of age, no recurrence of G.I. symptoms.
				Celiac syndrome (allergic?)	10 mos.	Persistent loose stools		"cured"	

TABLE I—*Continued*

Case No.	Name	Age (yrs.)	Sex	Allergic Symptoms			Intercurrent Illness	Remission Period	Comment
				Type	Duration	Severity			
9	C. S.	9	M	Asthma	6 yrs.	Moderate	Measles	5 mos.	Attacks every 1 to 3 weeks.
10	B. G.	4	F	Atopic dermatitis	3 yrs.	*Eczematous flexural rash+++	Measles	2½ weeks	First clearance in 3 years.
11	J. S.	4	M	Allergic rhinitis	2 yrs.	Constant nasal blockage	Measles	5 weeks	Remarkable clearance. "Better than any time during past 2 years."
12	P. L.	15	M	Asthma	14 yrs.	Severe	Scarlet fever and pneumonia	3 weeks	Almost daily attacks with frequent "status asthmaticus" for several months preceding onset of S.F. Temperature 104°F. for 4 days.
13	J. M.	16	F	Asthma	3 yrs.	Severe	Pneumonia	3 weeks	Daily attacks for 3 mos. prior to measles.
14	R. P.	1	M	Asthma	6 mos.	Attacks daily	Pneumonia	5 days	Pneumonia lasted 5 days during which there was dramatic clearance of rash and asthma. Gradual return of both during 2 weeks of convalescence.
				Atopic dermatitis	9 mos.	*Eczema++++		3 days	
15	J. S.	16	F	Asthma	15 yrs.	Severe	Upper respiratory infection with tonsillitis	11 days	"Only time without wheeze" in several years of constant intractable asthma. Concomitant skin clearance. Temperature 102°F. for 4 days.
				Atopic dermatitis	15 yrs.	*Eczema++++			
16	C. C.	1	M	Atopic dermatitis	8 mos.	*Eczema++++	Upper respiratory infection with tonsillitis	1 week	Temperature 104°F. for 2 days.

* Eczema+++ = moderately severe rash (atopic dermatitis).
* Eczema++++ = severe diffuse rash.

during the intercurrent infection; clearance and return of symptoms were concomitant.

The "anergic" phase usually became apparent at the height of the febrile period and continued for from five days to one year, the majority lasting a few weeks.

Historical

A review of the literature has produced many references to the phenomenon by which atopic symptoms are relieved temporarily by intercurrent

TABLE II

Summary of Previously Reported Clinical Observations

Author	Intercurrent Illness	Allergic Symptoms Relieved	Number of Subjects	Duration of Remission
Bookman[16]	Kaposi's varicelliform eruption (herpes simplex)	Atopic dermatitis (eczema)	1	7 days
Berg[15]	Lobar pneumonia	Asthma	2	First subject: free from asthma to publication date. Second subject: relief 4 mos. after first attack of pneumonia and to publication date after second attack.
Sidlick[18]	Tonsillectomy	Eczema (atopic dermatitis)	42	2 subjects indefinite (no known return of rash). 20 subjects: one to six months. 7 subjects: six mos. to one year. 6 subjects: one to two years. 6 subjects: two to three years. 1 subject: 3½ years.
Gorin[12]	3 operations on sinuses Appendectomy	Asthma	1	Relief for one month after each operation.
	Jaundice (infectious hepatitis)			10 weeks.
	Jaundice (serum hepatitis)	Asthma and atopic dermatitis	1	Free from symptoms to publication date.
	Jaundice (metastatic adenocarcinoma of liver)	Asthma	1	Marked improvement in asthma to publication date.
Boros[11]	Jaundice (cinchophen poisoning)	Hay fever	1	Free for two seasons (to publication date).
Feingold[7]	Measles	Atopic dermatitis	1	6 days.
	Measles	Atopic dermatitis	1	5 days.
	Measles	Asthma	1	12 days.
	Varicella Measles	Asthma	1	3 weeks. 3 weeks.
	Measles	Allergic rhinitis	1	12 days.
	Tonsillectomy Pertussis	Asthma	1	4½ mos. 2 mos.
	Varicella	Atopic dermatitis	2	1–2 weeks.
	Varicella	Allergic rhinitis	1	3 days.
	Mumps	Asthma	1	7 days.
	Roseola	Allergic rhinitis	1	5 days.
Fries and Borne[5, 6]	Kaposi's varicelliform eruption (vaccinia virus)	Atopic dermatitis	16	2–3 weeks.

infection or other altered physiologic states (pregnancy,[8-10] jaundice [11, 12] and surgery [13]).

Those reports detailed enough to permit analysis are listed in table 2. Seven authors are included and their 76 cases tabulated. It will be noted that five remissions followed measles; one author reports temporary remissions following tonsillectomy in 42 patients. Remissions observed ranged from a few days to several years.

In addition, such writers as Walzer,[1] Hill,[16] Sulzberger,[17] Norrlind [4] and Peshkin [18] have commented on the striking improvement in some allergic subjects following acute febrile infections.

Discussion

The temporarily beneficial effect of intercurrent febrile infections on the reactive allergic shock tissue would seem to be attributable to heightened—and sustained—temperature. This opinion has been voiced previously by others.[18] In our patients whose course was most affected (e.g., case 1), the temperature was higher and of longer duration than is usual for the infection involved.

Several reports on the favorable effect of induced fever on allergic disease have appeared in the past several years.[19-22]

Although other febrile illnesses, such as pneumonia [15] and tonsillitis,[4] have produced periods of refractoriness, measles would seem to be the most outstanding and consistent in its modification of the allergic process. Measles, characteristically, is a severe, systemic illness, usually with a prolonged period of fever, and includes a disseminated rash. Such cutaneous inflammation may induce dermal refractoriness resulting in improvement of the underlying allergic cutaneous disorder. The same explanation may account for the marked clearance of severe atopic eczema in our patients with infections due to vaccinia virus (Kaposi's varicelliform eruption).[5, 6, 14] Analogously, there is basis for this supposition in the clinical fact that cutaneous trauma or inflammation (e.g., sunburn) depresses the reactivity of the positive protein cutaneous test. Furthermore, inhibition of the cutaneous reaction to a tuberculin test performed during febrile illness, particularly measles, is well known.[23, 24]

Temporary suppression of the allergic response has actually been produced experimentally in the skin [25] and in the eye.[26]

There is considerable literature detailing the beneficial effects of measles on nephrosis,[27-29] producing normal states of such duration as to have been termed "cures." In this unexplained phenomenon there is an implied suggestion that nephrosis may be a form of hypersensitiveness, possibly bacterial.

Unfortunately, there is no constancy of beneficial effect of bacterial infection or of induced fever on the allergic state. On the contrary, with infections accompanied by slight elevations of temperature an adverse effect is more frequently seen.[7] The temporary nature of the mechanism is another

consideration. Almost without exception the symptoms recur. However, Berg [10] reported two adults with intractable asthma who obtained persisting relief following a severe attack of pneumonia. Gorin [12] observed two asthmatic patients and Boros [11] one asthmatic patient who remained apparently in complete remission after becoming jaundiced. Sidlick [13] noted two cases of eczema with complete remission following tonsillectomy.

The mediating factors that temperature, associated with infection, causes to be operative in these anergic states have yet to be determined. These have importance, since they may point to methods of alleviation of allergic symptomatology.

There are several possible explanations. The relief of allergic symptoms may be produced by some hormonal influence. It is possible that the heat regulating centers in the hypothalamus are bound up with the release of steroid hormones, producing an ACTH-like effect in humans.[30, 31] Selye [32] has referred to this mobilization of the endocrine defense mechanisms during fever. Or these beneficial alterations may possibly result from increased histaminolytic activity. Along these lines, Swanberg [33] accounts for the asymptomatic trend in the course of asthma during pregnancy by increased histaminolytic secretions in the blood.

The sudden interruption of frequently recurring asthma, or perennial rhinitis, or of a chronic, severe eczematous rash, and the refractoriness produced simultaneously in two widely different tissues, such as the lung and skin (as seen in the relief from asthma and eczema), would seem to negate coincidence as the factor involved.

Conclusions

1. Acute febrile infections, including measles and, more rarely, pneumonia and tonsillitis, can produce an anergic response in an allergic individual. This response is usually temporary. All but one of our patients relapsed after varying periods of time.

2. This inhibition of the allergic response does not unfailingly follow such febrile infections.

3. It would appear that the fever which accompanied the infection in the patients observed is the provocative factor in the remissions.

4. The striking improvement seen suggests that in this phenomenon of interference lies an investigative approach for the treatment of allergic disease.

BIBLIOGRAPHY

1. Walzer, M., *in* Coca, A. F., Walzer, M., and Thommen, A. A.: Asthma and hay fever in theory and practice, 1931, Charles C. Thomas, Springfield, Ill., p. 195.
2. Cooke, R. A.: Allergy in theory and practice, 1947, W. B. Saunders Co., Philadelphia, p. 130.
3. Tuft, L.: Clinical allergy, 1938, W. B. Saunders Co., Philadelphia, p. 75.
4. Norrlind, R.: Prurigo Besnier (atopic dermatitis), Acta dermat.-venereol. **26**: 62, 1946.
5. Fries, J. H., Borne, S., and Barnes, H. L.: Varicelliform eruption of Kaposi due to vaccinia virus complicating atopic eczema, J. Pediat. **32**: 532, 1948.

6. Fries, J. H., and Borne, S.: Vaccinial infection in children with atopic dermatitis, J. Allergy **20**: 222, 1949.
7. Feingold, B. F.: The influence of acute infection upon the course of allergy in children, J. Pediat. **34**: 545, 1949.
8. Berman, R. H.: Sarcoidosis benefited by pregnancy, J. A. M. A. **147**: 246, 1951.
9. Keller, P.: Beitrag zu den Beziehungen von Asthma und Ekzem, Arch. f. Dermat. u. Syph. **148**: 82, 1925.
10. Rost, G. A.: Die allergischen Hautkrankheiten, *in* Praktikum der allergischen Krankheiten, by Hansen, Karl, Rost, G. A., and Dekker, H., Stuttgart, 1930.
11. Boros, E.: Hay fever and asthma during and after jaundice, J. A. M. A. **109**: 113, 1937.
12. Gorin, N.: Temporary relief of asthma by jaundice, J. A. M. A. **141**: 24, 1949.
13. Sidlick, D. M.: The etiological relationship of tonsillar focal infection to eczema in children, M. J. and Rec. **128**: 344, 1928.
14. Bookman, R.: Kaposi's varicelliform eruption, report of a case treated with aureomycin and some observations regarding the course of the underlying skin disease, J. Allergy **21**: 68, 1950.
15. Berg, S.: Relief of bronchial asthma following lobar pneumonia, J. Allergy **2**: 54, 1930.
16. Hill, L. W.: Sensitivity to house dust and goose feathers in infantile eczema, J. Allergy **9**: 37, 1937.
17. Sulzberger, M. B., and Goodman, J.: The relative importance of specific skin hypersensitivity in adult atopic dermatitis, J. A. M. A. **106**: 1000, 1936.
18. Peshkin, M. M.: Asthma in children: incidence and significance of various diseases and infections, and of tonsillectomy and adenoidectomy, Am. J. Dis. Child. **33**: 880, 1927.
19. Miller, H., and Piness, G.: Hyperthermia induced by high frequency electric current in the treatment of intractable asthma, J. Allergy **2**: 436, 1931.
20. Leopold, S. S., and Stewart, S. G.: The effects of fever, either accidentally incurred or artificially produced, in bronchial asthma, J. Allergy **2**: 425, 1931.
21. Feinberg, S. M., Osborne, S. L., and Afremow, M. L.: Fever by diathermy in the treatment of allergic disease, J. Allergy **2**: 414, 1931.
22. Feinberg, S., Osborne, S. L., and Steinberg, M. J.: Sustained artificial fever in treatment of intractable asthma, J. A. M. A. **99**: 801, 1932.
23. Urbach, E., and Gottlieb, P. M.: Allergy, 2nd Ed., 1946, Grune and Stratton, New York, p. 515.
24. Rich, A. A.: The pathogenesis of tuberculosis, 1946, Charles C. Thomas, Springfield, Ill., p. 442.
25. Bowman, K., and Walzer, M.: The response of specific and histamine wheal sites in atopic skins to restimulation with specific and non-specific excitants, J. Immunol. **29**: 81, 1935 (abstracts).
26. Sherman, H., and Feldman, L.: Hypersensitiveness of the mucous membrane. IV. The effect of local reactions elicited by specific and nonspecific excitants upon the ophthalmic mucous membrane in allergic and nonallergic individuals, J. Allergy **15**: 77, 1944.
27. Blumberg, R. W., and Cassady, H. A.: Effect of measles on the nephrotic syndrome, Am. J. Dis. Child. **73**: 151, 1947.
28. Hutchins, G., and Janeway, C. A.: Observations on the relationship of measles and remissions in the nephrotic syndrome, Am. J. Dis. Child. **73**: 242, 1947.
29. Meizlik, E. H., and Carpenter, A. M.: Beneficial effect of measles on nephrosis, Am. J. Dis. Child. **76**: 83, 1948.
30. Kirdendall, W. M., Hodges, R. E., and January, L. E.: The ACTH-like effect of fever in man, J. Lab. and Clin. Med. **37**: 771, 1951.
31. Kass, E. H., and Finland, M.: ACTH and fever, New England J. Med. **243**: 693, 1950.
32. Selye, H.: The physiology and pathology of exposure to stress, 1950, Acta Inc., Montreal, p. 22.
33. Swanberg, A.: Asthma and pregnancy, Acta physiol. Scandinav. **16**: 83, 1948.

SERUM POTASSIUM PATTERNS IN ANURIA AND OLIGURIA *

By JAMES HOPPER, JR., *San Francisco, California,* BRIAN P. O'CONNELL, *Vancluse, New South Wales, Australia,* and HELLA R. FLUSS, *Montreal, Canada*

DANGEROUS elevation of serum potassium concentration is most frequently encountered clinically in patients suffering from anuria or oliguria.[1, 2, 3] In our experience, however, a dangerous rise in serum potassium concentration has been relatively rare. Such an elevation occurred in only six of a group of 15 of our patients with oliguria of three to 17 days' duration. In four of the six patients there were complicating circumstances which we believe were responsible for the high serum potassium levels. In the two remaining patients the high concentration could not be attributed to any factor other than the oliguria.

The pertinent features of potassium metabolism have been thoroughly reviewed.[4-8] They may be summarized as follows:

Intake: Nearly all foods contain potassium. Animal and plant cells and extracts made from them have the highest content. Tap water is practically free of this electrolyte.[9] The average daily intake on a normal diet varies from 42 to 135 mEq.[10]

Output: The greater portion of ingested potassium is absorbed from the small intestine. About 10 per cent of the intake is excreted in the feces, a small amount in the sweat, and the remainder in the urine.

Renal excretion of potassium depends upon maintenance of adequate glomerular filtration and renal tubular function. The amount of potassium excreted is a resultant of the amount filtered and of tubular re-absorption and excretion, both of which can occur.[11-15] Despite this combination of mechanisms, the renal control of potassium is not efficient when conservation of this electrolyte is at stake. The normal kidney, well able to conserve sodium in the face of depletion, is obliged to excrete potassium even when the concentration in the serum is low.[16, 17] An increase in the excretion of potassium is stimulated by dehydration.[16] This increase may relate to diminution of blood volume, since excretion also is increased when circulatory volume is reduced by hemorrhage, even when the concentration of potassium in the serum is low or normal.[18]

* Presented in abstract at the meeting of the American Federation for Clinical Research at Carmel-by-the-Sea, California, January, 1952. Received for publication December 2, 1952.

From the Department of Medicine, University of California School of Medicine, San Francisco, Calif.

This investigation was supported in part by a research grant, H-751, from the National Heart Institute of the National Institutes of Health, Public Health Service, and in part by a grant from the Herzstein Fund made by the University of California Medical Research Committee.

The adrenal cortical steroids [19] and the antidiuretic hormone of the posterior pituitary,[20] which also produce an increase in potassium excretion, affect the delicate adjustments in excretion as well.

Potassium of Cells and Extracellular Fluid

The bulk of the potassium of the body is contained within cells, where it is combined with protein and/or glycogen and where, in addition, it subserves osmotic pressure needs.[7, 21]

The normal concentration of potassium within cells is variously described as being between 112 mEq.[22] and 150 mEq.[21] per liter of cell water, whereas the concentration in the extracellular fluid and serum normally ranges between 3.5 and 5.3 mEq. per liter.[6]

In addition to the transfer of potassium associated with cellular metabolic processes, extensive movement of potassium into and out of cells occurs in a number of normal and abnormal circumstances. It is known that potassium leaves the cells in conditions of stress, such as severe shock and anoxia and agonal and postoperative states, during muscular contractions, and also during the rapid breakdown of tissue such as occurs in involution of the uterus and in uncontrolled diabetes mellitus and other types of starvation.[7] Potassium is also liberated from cells into the extracellular fluid in alkalosis.[8] Interestingly, a rise in the concentration of potassium in the extracellular fluid has also been reported in acidosis.[23, 24] Cellular transfer of potassium is influenced by a variety of hormones. Insulin, epinephrine [7] and androgens [25] tend to cause movement of potassium into cells, whereas certain of the adrenal corticoids produce the reverse effect, as does corticotrophin.[6, 26]

Cells take up potassium during protein and carbohydrate anabolism, in the paralytic phase of familial periodic paralysis, during administration of potassium (particularly in states of potassium depletion), and during treatment of adrenal cortical insufficiency with adrenal cortical hormones.[4, 19, 26]

It is difficult to be certain whether changes in cellular potassium concentration are deleterious to the organism. Most of the symptoms of potassium excess or lack appear to be related to the rise or fall of the concentration in the serum. Clear-cut evidence of harm resulting from an increase in cellular potassium content is wanting.[27] It further appears that cellular potassium concentration does not rise above normal unless the level in the serum is also high.[28, 29]

Clinical Effects of Hypopotassemia and Hyperpotassemia

The effects of a low level of serum potassium, which can be reversed by administration of potassium, have been summarized by Darrow [5] as follows: (1) electrocardiographic changes—low and inverted T waves, depressed ST interval and prolonged QT interval; (2) weakness of the extremities, depression and loss of muscle tone and of deep tendon reflexes; (3) paralysis of the limbs, and occasionally of the trunk muscles; (4) paralytic ileus,

vomiting, and possibly diarrhea; (5) alkalosis and, less certainly, (6) edema and low concentration of serum albumin, and (7) cardiac dilation and failure, also with edema.

In hyperpotassemia, that is, when the serum potassium concentration exceeds 5.3 mEq. per liter, the neuromuscular system in general is affected.[30, 31] The most striking changes, however, occur in the heart and can be demonstrated by electrocardiogram. While the serum potassium levels at which these changes occur are regularly reproducible in the experimental animal, this is by no means true clinically. The first sign of toxicity is an elevation and peaking of the T wave; in dogs with pure potassium intoxication, it occurs between serum levels of 5.0 and 7.8 mEq. per liter.[32] Tarail found that in man the onset of this change is extremely variable, but that T wave changes were always found when the serum potassium concentration exceeded 6.8 mEq. per liter.[8] Later signs are widening of the QRS complex and depression of the ST segment; as serum potassium levels increase, cardiac conduction becomes more depressed, auricular standstill occurs and P waves disappear. Still later the QRS complex becomes wider and biphasic, irregularities of rhythm appear and, if the serum potassium concentration continues to rise, progressive heart block finally leads to cardiac arrest in diastole. The level at which this occurs is extremely variable. In dogs,[32] cardiac arrest was observed consistently when levels exceeded 14.3 mEq. per liter, whereas in patients with renal insufficiency who had developed other electrolyte disturbances, fluid compartment distortion and nitrogen retention, we have found cardiac arrest at serum levels as low as 9 mEq. per liter.

Selection of Patients and Methods

Potassium metabolism was studied in 15 patients with oliguria of three to 17 days' duration. A number of these patients had acute tubular necrosis (so-called lower nephron nephrosis),[33] while others manifested urinary suppression of indeterminate origin, as described by Stock.[34] According to Stock, a patient is oliguric if his urinary output is insufficient to prevent accumulation of excretable solids.

This particular group was selected for study from a larger group of patients with oliguria because we had made frequent determinations of the serum potassium levels during the oliguric phase in all 15 patients. These cases were not chosen to demonstrate the effectiveness of conservative treatment as advocated by us[35] and others. In fact, they portray the grim features of this condition.

Although some of the patients were seen in other hospitals, serum sodium and potassium concentrations were determined in all instances at the University of California Hospital. The lithium internal standard flame photometer, as described by Hald,[36] was used in these determinations. Other tests included measurement of serum calcium,[37] inorganic phosphorus[38] and chloride concentrations,[39] and carbon dioxide capacity.[40]

The majority of the 15 patients were treated according to the method for the management of patients with oliguria and severe renal insufficiency described in a previous report.[35] The method of treatment during the oliguric and postoliguric stage may be summarized as follows:

Oliguric Stage: 1. Activity, fever and other factors which promote increased catabolism are controlled to prevent rapid accumulation of catabolites.

2. A diet high in carbohydrate and low in protein, with a controlled electrolyte content and with vitamin supplements, is instituted. At least 150 to 200 gm. of carbohydrate in divided doses are given daily at six to eight hour intervals. Additional carbohydrate is given if fluid requirements permit. Food must be administered parenterally if it is not retained when given by mouth. At times we have modified this regimen by giving a Borst diet [41, 42] by stomach tube. A stomach-tube feeding may result in drowning if the patient is unconscious and vomiting occurs. This diet has produced diarrhea in some of the patients we have treated; if, however, it is desirable to get rid of potassium, this is not unfavorable.

3. Sufficient fluid is given to maintain the patient at his usual "good" pre-illness weight. At the same time, an attempt is made to control the fluid compartments of the body and to maintain them as near normal as possible. Transfusions of whole blood or red blood cell mass are given if necessary.

Fluid, nutritional and electrolyte needs are determined individually; the components are pooled to give a resultant, which establishes the concentration and composition of any fluid to be administered. The concentration and composition, in turn, indicate the route of administration. For example, on a particular day a patient may require 400 ml. of fluid, 100 mEq. of sodium and 150 gm. of glucose. This amount of sodium and glucose in 400 ml. of water forms a strongly hypertonic solution which, if given parenterally, can only be administered intravenously. In the example given, the requirements can be met by giving three infusions of 100 ml. of 50 per cent glucose in water at intervals of eight hours, and 100 ml. of 1 molar sodium lactate solution.

4. Electrolytes are controlled to maintain a normal state with respect to (a) osmotic pressure (sodium), (b) acid-base balance, and (c) pharmacodynamic action. An attempt is made to maintain electrolyte concentration as near normal as possible by supplying deficient electrolytes and withholding or removing electrolytes whose concentration in the body fluids is too high. Because sodium has an osmotic effect, it cannot be given in quantity sufficient to combat acidosis effectively in patients with anuria. Therefore, carbohydrate must be used liberally for its acidosis-preventing properties. We have not found it necessary to give potassium until oliguria has ceased, but it is frequently necessary to combat hyperkalemia by forcing carbohydrate (usually as glucose) or by other means, such as use of exchange resins in the form of enemas.[43] One of the several procedures by which potassium can be dialyzed from the blood stream may be required in particular instances.

5. Congestive heart failure is treated with digitalis. The measures are the same as those used to control congestive heart failure uncomplicated by renal insufficiency. Full dosage of digitalis is used.

6. In treatment, drugs which are excreted exclusively by the kidneys are not used; if for any reason they must be given, great caution is required.

7. Convulsions are treated, when necessary, by administration of anticonvulsant drugs which do not demand renal excretion.

Postoliguric Stage: 8. Fluids are forced within limits determined by circulatory competence and renal ability to excrete an increased fluid volume. Care should be taken not to force fluids and sodium to the point where weight gain is produced. This may be guided by frequent weighing of the patient. Since excessive loss of electrolytes may occur during diuresis, care is taken to replace lost electrolytes (especially sodium and potassium).

9. High caloric and normal protein intake are quickly reëstablished.

Results

The data relating to the potassium metabolism of the 15 patients studied are shown in figures 1 and 2. Further details concerning these patients are summarized in table 1. The patients were divided into two groups on the basis of whether the concentration of serum potassium was or was not "dangerously" high.

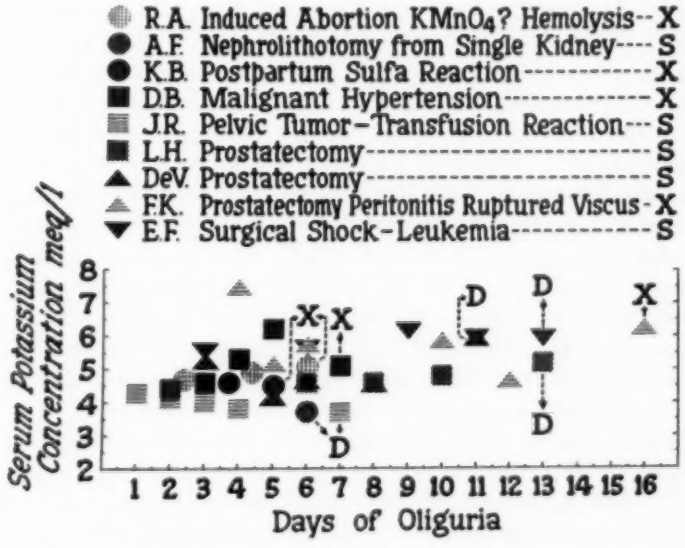


Fig. 1. Group I: Nonelevated serum potassium patterns. X = Death. S = Survival. D = Diuresis of 1,000 c.c. or more.

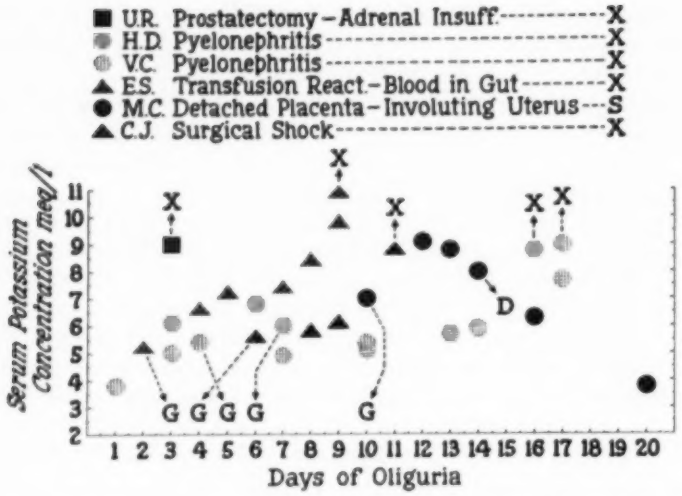

U.R. Prostatectomy – Adrenal Insuff. X
H.D. Pyelonephritis X
V.C. Pyelonephritis X
E.S. Transfusion React. – Blood in Gut X
M.C. Detached Placenta – Involuting Uterus S
C.J. Surgical Shock X
Serum Potassium Concentration meq/l
Days of Oliguria
G
D

FIG. 2. Group II: Elevated serum potassium patterns. X = Death. S = Survival. D = Diuresis of 1,000 c.c. or more. G = Glucose infusions begun (see text).

Group I (figure 1) was composed of nine patients in whom, with one exception, the serum potassium concentration did not rise above 6 mEq. per liter. As shown by the data in figure 1, a dangerous elevation in serum potassium concentration does not necessarily occur, even when oliguria is prolonged (16 days in one patient) during treatment with conservative methods. The one patient (F. K.) in whom serum potassium concentration was initially high (7.4 mEq. per liter) developed peritonitis following prostatectomy with rupture of the bowel. After surgical drainage of five pints of blood and feces from the peritoneal cavity, the serum potassium concentration in this patient fell to 4 mEq. per liter and remained relatively low; on the day the patient died it was only 6 mEq. per liter. It is further notable that in the four patients who died (figure 1), serum potassium concentrations on the day of death or, in one instance, the day before death, were 6 mEq. per liter or under. In the five patients who did not die, diuresis of 1,000 ml. or more occurred on the seventh day of oliguria in two subjects, on the eleventh day in one, and on the thirteenth day in two.

Group II (figure 2) was composed of six patients in whom the concentration of serum potassium rose to levels usually considered dangerously high.[8, 32] One patient (M. C.) developed acute tubular renal insufficiency following abruptio placentae near term. It is of interest that this patient survived, inasmuch as she showed a potassium concentration of 9.1 mEq.

TABLE I

Summary of Pertinent Clinical Data in 15 Patients with Anuria or Oliguria

Patient	Age (yrs.)	Sex	Duration of Urine Suppression (days)	Daily Urinary Vol. ml. during Suppression		U/P Ratio* Creatinine	Serum* Creatinine (mg./100 ml.)	Blood* NPN (mg./100 ml.)	Day of Death from Onset of Oliguria	Maximal Serum K* Concentration† (mEq./L.)	Serum Na* Concentration† (mEq./L.)	Average Urinary* K Excretion (mEq./24 hr.)	Diagnoses
				Average	Range								
1. R. A.	40	F	6	55	45-65	— —	— —	220 (6)	6	5.1 (6)	157		Induced abortion. Transfusion reaction?
2. A. F.	46	M	6	450	290-635	— —	17.1 (9)	175 (12)	Survival	3.7 (6)	130		Post nephrectomy. Acute urinary suppression following nephrolithotomy of remaining kidney.
3. K. B.	14	F	6	290	180-700	7.9 —	13.4 (4)	194 —	6	4.6 (4)	136		Postpartum. Sulfadiazine reaction; arteritis; acute tubular necrosis; acute cor pulmonale. Death from right ventricular heart failure.
4. D. B.	42	F	7	265	0-500	14.2 —	3.8 (−5)	240 (7)	7	6.2 (5)	126		Essential malignant hypertension. Cardiovascular disease.
5. J. R.	63	M	7	600	250-985	— —	— —	165 (5)	Survival	4.3 (1)	128	20.0 (10)	Transfusion reaction? Acute tubular necrosis; partial ureteral obstruction due to neoplasm.
6. L. H.	55	M	12	363	175-800	5.7 (9)	23.0 (9)	177 (15)	Survival	5.2 (13)	141	36 (12-14)	Transurethral resection. Acute tubular necrosis.
7. De V.	65	M	10	495	400-660	5.1 (11)	16.4 (11)	187 (11)	Survival	5.2 (3)	132	164 (17)	Transurethral prostatectomy. Acute tubular necrosis.
8. F. K.	67	M	16	112	70-165	— —	17.8 (12)	590 (12)	16	7.4 (4)	130		Transurethral prostatectomy. Hemorrhage; shock; acute tubular necrosis.
9. E. F.	53	F	12	See Fig. 3	—	— —	18.2 (10)	218 (15)	Survival	6.2 (9)	136	6.3 (5-12)	Leukemia. Splenic rupture; shock; acute tubular necrosis.
10. R. U.	58	M	3	—	—	— —	— —	— —	3	9.0 (3)	128		Transurethral resection. Hemorrhage; shock; acute tubular necrosis.
11. H. D.	75	F	16	120	0-200	2.2 (13)	23.2 (13)	— —	16	8.8 (16)	145	1.9 (11-16)	Chronic pyelonephritis. Hypertensive cardiovascular disease.
12. V. C.	35	F	17	134	30-370	5.1 (3)	19.2 (3)	338 (17)	17	9.0 (17)	122	0.4 (10)	Chronic pyelonephritis. Hypertensive cardiovascular disease.
13. E. S.	64	M	9	150	20-685	6.4 (8)	22.4 (8)	315 (9)	9	10.9 (9)	142		Portal hypertension. Portocaval anastomosis; acute tubular necrosis.
14. M. C.	22	F	15	See Fig. 4	—	2.7 —	21.8 (15)	330 (17)	Survival	9.1 (11)	128	63.0 (16-18)	Abruptio placentae. Acute tubular necrosis.
15. C. J.	53	M	11	330	160-500	4.1 (8)	18.4 (8)	79 (3)	11	8.8 (11)	122	14.3 (6-9)	Traumatic arterial aneurysm. Surgical shock; transfusion reaction? Acute tubular necrosis.

* Figures in parentheses indicate the number of days from onset of urinary suppression (column 4) and the day upon which the determination was made. † Serum K and Na determinations on identical sample.

per liter, the second highest value observed in any of the 15 patients (figure 3). In addition, the electrocardiographic patterns typical of developing potassium intoxication, which were observed in this patient, were reversed when she received digitalis, in spite of a rising concentration of potassium in the serum (figure 4).

In our opinion this spectacular rise in serum potassium concentration was related to involution of the uterus and possibly to a hemolytic process, inasmuch as transfusion with large amounts of blood failed to produce the usual rise in hemoglobin (figure 3). Fecal urobilinogen was not tested, but it is assumed that the liver effectively handled the pigments resulting from blood breakdown, since the icterus index was not elevated at any time. There were no signs of overt hemorrhage, beyond the bleeding that occurred

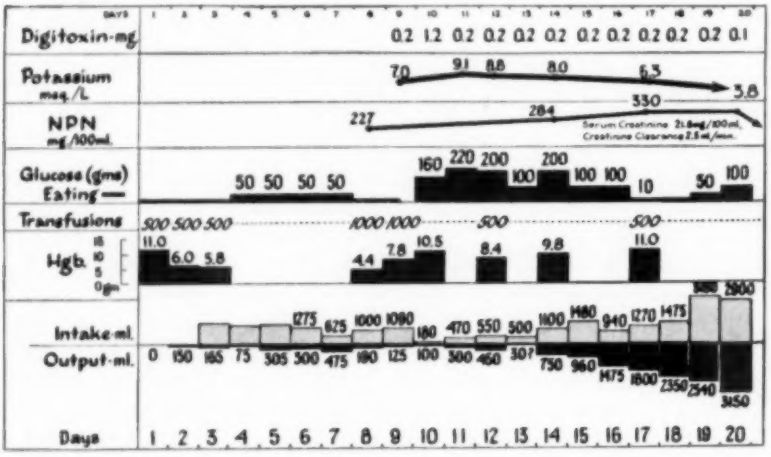


FIG. 3. Patient M. C.: High serum potassium concentration with survival in acute tubular necrosis following premature placental separation.

initially with detachment of the placenta and with the Cesarean section; the hemorrhage which occurred in lochia was considered less than usual. Inasmuch as this patient's systolic blood pressure never fell below 90 mm. Hg, it would appear that blood had been diverted away from the kidneys to more vital areas. A recent article [11] has summarized the events which lead to acute tubular injury during such demands, despite reasonably well maintained blood pressure.

In three of the remaining five patients in the second group, all of whom died, the rise in serum potassium concentration could be related to special circumstances likely to cause a rise in extracellular fluid concentration of potassium.

Patient U. R. developed acute tubular renal necrosis following trans-

urethral prostatectomy and died on the third postoperative day, which is sooner than death usually occurs in a patient with an uncomplicated tubular lesion. Serum potassium concentration rose precipitously and reached 9 mEq. per liter on the second postoperative day, which was the third day of oliguria and the day of death. At autopsy, the adrenals were described as exhausted, and partial necrosis was noted in one gland.

Patient H. D., who had long-standing pyelonephritis, developed a severe bleeding tendency such as occurs frequently in patients with severe renal insufficiency.[35, 45, 46] She died on the sixteenth day of oliguria, at which time the serum potassium concentration was 8.8 mEq. per liter. During the last two days of life a bloody diarrhea was noted. Postmortem examination revealed extensive ecchymoses in the superficial tissues of the

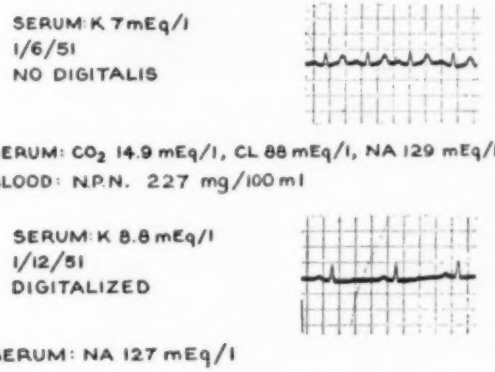


FIG. 4. Patient M. C.: Electrocardiographic signs (Lead II) of beginning potassium intoxication at serum potassium concentration of 7 mEq. per liter. Absence of potassium intoxication at 8.8 mEq. per liter.

body, extensive ecchymosis of the gastrointestinal tract, and the presence of large amounts of blood in the intestine.

Patient E. S. also showed extensive bleeding into the gastrointestinal tract. In this patient a portocaval anastomosis had been performed for the treatment of portal hypertension. During operation he received one and one-half units of blood. (The second unit was discontinued because he developed a febrile reaction.) Following the operation the patient was oliguric. The results of urinalysis were consistent with acute tubular necrosis, and the blood reflected retention of nitrogenous end products. On the eighth postoperative day, which was also the eighth day of oliguria, the serum potassium reached a concentration of 8.4 mEq. per liter. At this time an electrocardiogram demonstrated an I-V conduction defect, as expressed

by a slurred QRS interval of 0.13 second and a depressed ST segment, with inverted deep T waves and absent P waves. On the day of death, the ninth day of oliguria, the serum potassium concentration was 10.9 mEq. per liter. An electrocardiogram taken five hours before death, when the serum potassium level was 9.8 mEq. per liter, showed an irregular rhythm, with a rate of approximately 44, a QRS interval of 0.12 second, slurred throughout, a depressed ST segment with an inverted T wave in Leads II, III, and AVF, a QT interval of 0.38 second, tall sharp T waves in Leads V_2 and V_3, and an absence of P waves. Infusion of glucose solution was ineffective in decreasing extracellular fluid potassium concentration, as were potassium exchange resin enemas [43] administered in the last 24 hours of life. Autopsy

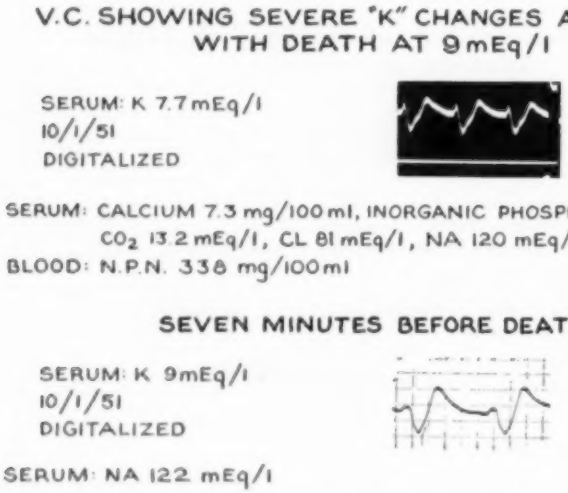


FIG. 5. Patient V. C.: Electrocardiographic signs (Lead II) of severe potassium intoxication at relatively low serum potassium concentrations in pyelonephritis with oliguria.

examination revealed massive hemorrhage filling the entire small bowel, which probably resulted during the last few days of oliguria from rupture of esophageal varices.

In two other cases (V. C. and C. J., shown in figure 2; also see table 1), the rise in serum potassium concentration level could not be related to any special circumstance known to cause potassium release.

Patient V. C. had chronic pyelonephritis and died on the seventeenth day of oliguria. Serum potassium concentration rose rapidly during the day from 7.7 to 9.0 mEq. per liter one-half hour before death. It is remarkable that the concentrations of other extracellular fluid electrolytes were also abnormal (figure 5). Autopsy examination showed no apparent cause for

the elevation of serum potassium concentration, except for the fact that the kidneys were extremely atrophic.

Patient C. J. developed acute tubular insufficiency after surgical removal of an aneurysm of a right axillary artery, which had developed following a gunshot wound a month before. During operation the patient received 1,500 ml. of compatible donor blood and 700 ml. of autotransfused blood. The systolic blood pressure dropped and remained at 50 mm. Hg for 20 minutes. The operation lasted for six hours; anesthesia was nitrous oxide and oxygen, and sodium pentothal. His blood pressure remained relatively low the next 12 hours, but rose after further transfusion. On the second postoperative day the patient appeared cyanotic and slightly dyspneic. He complained of pain in the right side of the chest. Signs of fluid in the right chest cavity led to removal of 1,000 ml. of serosanguineous fluid, which possibly had resulted from pleural rupture during the operation and subsequent bleeding. Although conservative treatment induced temporary improvement, the patient's condition took an unfavorable turn on the ninth postoperative day, which was also the ninth day of oliguria. Death ensued on the eleventh day. The serum potassium level was 8.8 mEq. and the sodium concentration 122 mEq. per liter approximately 12 hours before death. Autopsy was performed by a coroner. His report contained no information regarding the presence of blood in the right pleural cavity.

Case Illustrating Conservative Medical Management: Figure 6 illustrates the medical management of an oliguric patient. This patient, E. F., had leukemia. She suffered a ruptured spleen 14 days after a splenic needle biopsy was performed, which resulted in considerable loss of blood into the peritoneal cavity and accompanying shock. The spleen was removed surgically, and free blood was withdrawn from the peritoneal cavity. Despite extensive transfusions both before and after operation, the patient remained in shock, and her blood pressure fell as low as 50/40 mm. Hg. Following operation, no urine could be obtained from the urinary bladder (day 1, figure 6); oliguria continued until the eleventh postoperative day. Liberal infusions of glucose solution were given parenterally, as indicated, and food was withheld until the seventeenth day, when the patient was able to retain food given by mouth. It is notable that the serum potassium concentration reached a peak level of 6.2 mEq. per liter on the ninth day of oliguria, and that it was necessary to give potassium when the serum potassium level fell to 2.5 mEq. per liter in the postoliguric period. At this time the patient was inordinately weak, and had attained an output of 4,450 ml. of urine in 24 hours. Although not shown in figure 6, fluid was restricted initially to reduce the patient's weight to 58 kg., her preoperative "good" weight, after which fluid intake was increased rapidly to meet the renal ability to excrete a larger volume of urine. The continued rise of blood nonprotein nitrogen during periods of tubular insufficiency, even when urinary volume is rapidly increasing, has been frequently observed by our-

selves and others. The response of this patient to treatment is typical of the patients in Group I (figure 1) who survived, and also of other patients we have observed (not reported here) who survived a period of oliguria.

Case Illustrating Potassium-Digitalis Relationships: Figure 4 shows the electrocardiographic changes manifested by patient M. C. during a period of tubular insufficiency after premature placental separation. The first electrocardiogram was taken before digitalization of the patient. The first determination of serum potassium, taken three days later, showed a concentration of 7.0 mEq. per liter (figure 3). It will be noted that beginning potassium intoxication is suggested by the electrocardiographic pattern of high amplitude T waves approaching the height of QRS complexes, with

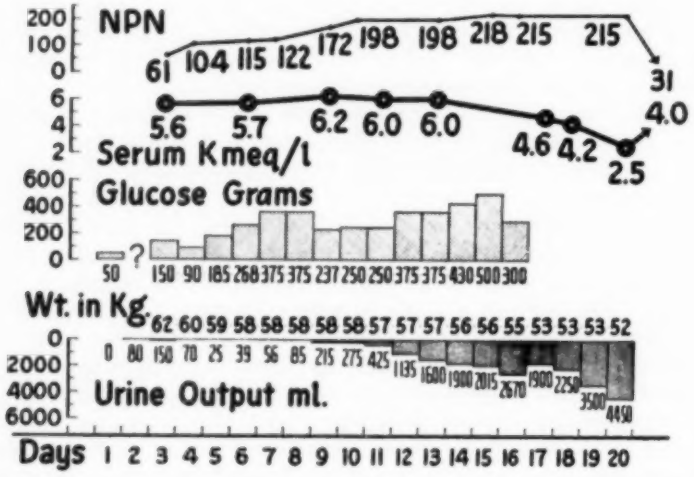


FIG. 6. Medical management of oliguria in leukemic patient (E. F.), with acute tubular insufficiency following surgical shock.

so-called tenting of the T waves.[47] Subsequently, it was discovered that the blood hemoglobin level had fallen to 4.4 gm. per 100 ml.; therefore, transfusions totaling 2,000 ml. of whole blood were given. Signs of congestive heart failure (increased venous pressure and pulmonary congestion) appeared after the transfusions. Accordingly, the patient was digitalized; she received 1.4 mg. of digitoxin in the first 12 hours, and 0.2 mg. daily thereafter (figure 3). Cardiac compensation resulted within 24 hours and was well maintained, despite continued renal insufficiency.

A second electrocardiogram was taken on January 12, 1952. At this time the serum potassium concentration, which had been 9.1, had fallen to 8.8 mEq. per liter. Despite the high concentration of potassium in the serum, the amplitude of the T waves in Lead II was diminished, as might

be expected after the administration of digitalis (figure 4). (Inasmuch as the patient was in a private hospital, frequent electrocardiograms were not taken.)

It is interesting to contrast the electrocardiographic tracings of patient M. C. with those of patient V. C. At a time when both patients had nearly identical serum potassium concentrations, V. C. showed electrocardiographic signs of severe potassium intoxication (figure 5), whereas M. C. showed only mild changes attributable to potassium effect (figure 4). In V. C. on the same day, which was the day of death, abnormality of the other extracellular fluid electrolytes was shown by the following measurements: serum calcium, 7.3 mg. per 100 ml.; inorganic phosphorus, 14.8 mg. per 100 ml.; serum carbon dioxide capacity, 13.2 mEq. per liter; and serum chloride and serum sodium, 81 and 120 mEq. per liter, respectively. Expanded extracellular fluid volume was evidenced by moderate edema. In this patient, efforts to effect a rise in serum sodium concentration by administering a hypertonic solution of sodium chloride increased the edema without raising the extracellular fluid sodium concentration.

Discussion

The 15 cases reported in this study were characterized by extremely low urinary plasma ratios of creatinine and low creatinine clearances (table 1). In nine of the 15 patients the rise in serum potassium concentration was not notable, despite the presence of severe renal insufficiency and oliguria (figure 1).

Our observations are by no means unique in this respect. Welt and Peters [44] reported the case of a woman (B 76793) with carcinomatous obstruction of both ureters. Although the patient was "virtually completely anuric for 35 days," the serum potassium concentration six days prior to death was only 3.6 mEq. per liter. Stock [34] also reported a case of a 31 year old woman (G. M.) with ureteropelvic obstruction and urinary suppression of 50 days' duration. The serum potassium concentration in this patient was only 5.7 mEq. per liter "prior to death." (The interval prior to death is not given.) Of the 22 patients reported by Stock, 11 died. The fact that potassium intoxication may have been implicated in certain instances is impossible to prove, since figures on potassium concentration were not given. In other instances, it is clear that the patients died of causes unrelated to potassium intoxication. Borst [41] kept nonuremic patients for 22 days on the protein-free diet he advocates in severe uremia. He found that the amount of potassium excreted by these subjects, if retained, would have been insufficient to produce toxicity.

The ability of carbohydrate to prevent accumulation of potassium in the extracellular fluid appears to be demonstrated by the majority of our patients. Unfortunately, data on a control group of oliguric patients are not

available; in view of the precarious condition of our patients, we were disinclined to withhold carbohydrate as an experiment.

In four of the six patients who showed high serum potassium concentrations during renal insufficiency accompanied by oliguria (figure 2), special circumstances apparently accounted for the rise. The rapid increase in serum potassium concentration during the last day of life in one of the remaining two patients (V. C.) was possibly an agonal phenomenon. It is of interest that all of the patients who died, whether the serum potassium concentration was relatively low or was high, evidenced a marked retention of nonelectrolytic catabolites, as well as severe derangement of electrolytes other than potassium and often of the fluid compartments of the body. Numerous reports have shown that administration of carbohydrate causes a shift of potassium from the extracellular fluid into the cells to meet the needs of glycogen deposition, and thus is effective in reducing extracellular fluid potassium concentration.[5, 7, 21, 48-52] Our data appear to support this evidence. In addition, it has been demonstrated that glucose, by promoting cell metabolism, can cause potassium to enter cells without the need for glycogen deposition.[53] Our data (table 1, column 12), like those of other investigators,[15, 53] show that in severe renal insufficiency only a negligible amount of potassium is excreted when the urinary volume is small, whereas when the volume is large the loss of potassium is also greater. Thus, renal excretion of potassium cannot be held responsible for the low serum potassium concentrations observed in most of our patients in Group I. Note that in the case of E. F. (table 1, case 9), in whom the maximal concentration of serum potassium measured 6.2 mEq. per liter, the average urinary excretion of potassium from the fifth through the twelfth day of oliguria was only 6.3 mEq. per liter. Clearly, then, the fact that the concentration of potassium in the serum did not rise could not be attributed to excretion of potassium in the urine.

Of the nine patients in whom the serum potassium concentration did not exceed 6 mEq. per liter (figure 1), five survived and four died. The fact that those who died had relatively low serum potassium concentrations strongly supports the idea that death did not in any way relate to potassium concentration alone, but must have been related to other factors associated with renal insufficiency and oliguria.

The mechanism of death in oliguria is obscure. One wonders whether potassium becomes toxic when there is derangement of other electrolytes, such as sodium, or accumulation of organic catabolites (that is, whether the toxic effect is synergized); or whether, under certain circumstances, accumulation of intracellular potassium becomes dangerous; or whether it is the derangement, imbalance or accumulation of other electrolytes or catabolites which leads to death. Very high serum potassium concentrations have been withstood temporarily by patients depleted of potassium who were given potassium-containing fluids. Govan and Weiseth[54] described an infant with infantile diarrhea who survived a serum potassium level of 12.27

mEq. per liter, and Currens and Crawford [55] reported the case of a 42 year old woman with hypopituitarism and adrenal insufficiency who survived a concentration of 12.7 mEq. per liter. In these patients, electrocardiograms showed signs considered typical of severe potassium toxicity. In normal dogs, Winkler, Hoff and Smith [32] found that death usually did not occur until a serum potassium concentration of 14.3 mEq. per liter was reached.

Clearly, then, high serum potassium concentrations can be survived under certain circumstances. Other factors, however, appear to have been implicated in the case of the nine patients in our group who died, since one had a serum potassium concentration below 6 mEq. per liter the day before death, four had concentrations of 6 mEq. per liter or below on the day of death, three had concentrations of 9 mEq. per liter or below on the day of death, and only one had a concentration above 9 mEq. per liter (10.9) at death (figures 1 and 2).

Inasmuch as the end products of catabolism are acid, and the ability to excrete acids is limited in oliguria, it is possible that acidosis, either in relation to potassium or otherwise, may contribute to the demise of oliguric patients. In the electrocardiograms of patients with diabetic acidosis, Nadler, Bellet and Lanning [24] demonstrated that the height of the T waves varies inversely with the pH of the blood and the serum carbon dioxide content. A recent experimental study [23] reported that plasma potassium concentrations rose when dogs were made acidemic by administration of ammonium chloride, and fell when they were made alkalemic by administration of sodium bicarbonate, and that the changes inversely paralleled the pH. Concomitantly, amplitude of the T waves was diminished by administration of alkali and increased by the administration of acid.

It has long been known that calcium promotes more vigorous systole, and that potassium increases diastolic relaxation of the heart.[56, 57] Accordingly, calcium has frequently been administered for the purpose of opposing potassium intoxication.[54, 58, 59] Recent studies on the frog heart [60] have suggested that there is an optimal potassium concentration at which cardiac contractility is always maximal. At a fixed calcium concentration, increase of potassium above or below the optimal level causes a diminution of contractility. At optimal potassium concentrations, variations in the concentration of calcium will augment or decrease contractility. The authors concluded that cardiac contractility does not depend upon the calcium-potassium ratio of heart muscle. This subject has been reviewed recently.[61] It is of interest that in one of our patients (V. C., figure 5), electrocardiographic evidence of severe potassium toxicity, which occurred when the serum potassium concentration was 7.7 mEq. per liter, calcium 7.3 mg. per 100 ml., and total serum protein 5.6 gm. per 100 ml., showed temporary reversal of the signs of toxicity after intravenous administration of calcium gluconate. The effect of calcium and sodium depletion in potassium intoxication has been the subject of recent study.[2, 47] The conclusions of these authors support our observations that the electrocardiographic signs of potassium in-

toxication appear to be influenced by the concentration of other electrolytes. Although sodium concentration was carefully followed in all of our cases, no correlation between potassium toxicity and the state of sodium was apparent (table 1).

In our studies, like those of Tarail [8] and others,[24, 47] the electrocardiographic changes associated with potassium intoxication occurred at variable concentrations. These changes are said to result invariably in man when serum potassium levels rise to 7 mEq. per liter or higher.[8] While this hypothesis has been questioned,[2] it does appear to be true in dog heart-lung preparation.[62] Accordingly, the changing electrocardiographic pattern shown by M. C. (figure 4) before and after digitalization during the period when the extracellular fluid potassium concentration was rising is of particular interest. The effect of digitalis and potassium on heart action [61] and the effect of potassium upon cardiac arrhythmias have been the subject of study.[63, 65] Cardiac glucosides have been found to protect normal animals from potassium poisoning and to lower the concentration of serum potassium in adrenalectomized animals.[66] In dog heart-lung preparations, electrocardiographic signs of potassium intoxication can be reversed or instituted at will by increasing or decreasing the dose of digitalis.[67] In patient M. C., the development of a pattern consistent with digitalis action rather than with potassium intoxication (lower tracing, figure 4) at a time when the serum potassium level was 8.8. mEq. per liter suggests that the heart was protected from the effects of excess potassium.* Further studies are needed in which the effects of digitalis are titrated against the effects of potassium intoxication. It is our distinct impression, however, that in patient M. C. the heart was protected from the toxic effects of potassium by digitalis. The fact that potassium depletion results in increased susceptibility of the heart to digitalis effects also has been shown.[68, 69] Inasmuch as we believe that anuric and oliguric patients require full digitalization and maintenance doses,[35] we have wondered if the reason why oliguric patients are able to withstand full doses of digitalis may not be related to their tendency to have relatively high levels of extracellular and/or cellular fluid potassium.

Summary

Fifteen patients with oliguria, due in most instances to acute tubular necrosis (lower nephron nephrosis), were made the subjects of this study because their serum potassium concentrations had been followed throughout the clinical course of oliguria.

Death occurred in nine of these patients. Serum potassium concentrations were not elevated in four of the subjects and could not be implicated in their deaths; they were only mildly elevated in two patients, and moderately high in the remaining three.

* By personal communication, J. J. Sampson and K. A. Klinghofer have reported similar observations of reversal of potassium intoxication by administration of digitalis in a patient with oliguria.

The concentrations of other electrolytes and catabolites and the fluid volumes were often abnormal. These derangements were believed to have either caused or contributed to the deaths of the nine patients. It was not possible to relate potassium effect to disordered sodium concentration in our cases.

In one of the six surviving patients, the serum potassium level (9.1 mEq. per liter) was the second highest concentration found in the 15 patients. Electrocardiographic signs of developing potassium toxicity were reversed during administration of digitalis in full dosage, although the serum potassium concentration at that time was 8.8 mEq. per liter. This experience supports observations that digitalis and potassium have certain opposing effects upon the heart. Accordingly, it is suggested that in some instances the toxic effects of hyperkalemia upon the heart may be effectively opposed with digitalis.

The fact that oliguric and/or anuric patients require full digitalization and full maintenance doses of digitalis and that signs of digitalis toxicity are rare in patients so treated suggests that tolerance of digitalis in such cases is mediated by the opposing effect of potassium.

While many patients with acute tubular necrosis can be treated by conservative medical means, the occurrence of excessive hyperkalemia may require the use of more drastic measures, such as vividialysis or the use of potassium-removing exchange resins.

Inasmuch as the electrocardiogram does not always accurately reflect serum potassium concentrations, care of oliguric patients should be undertaken only in hospitals where facilities for measurement of serial potassium concentrations are available.

ACKNOWLEDGMENTS

We wish to thank Dr. T. L. Althausen, Dr. H. Glenn Bell, Dr. Frank Hinman, Jr., Dr. Frederick Howard, Dr. S. P. Lucia, Dr. Emmett Taylor, Dr. Herbert Traut and Dr. Harold Watson for their courtesy in allowing us to study the patients in this report. We should also like to thank Dr. Nobuyuki Kawata for his skilful treatment and study of patient E. F. (figure 6).

BIBLIOGRAPHY

1. Elkinton, J. R., Tarail, R., and Peters, J. P.: Transfers of potassium in renal insufficiency, J. Clin. Investigation **28**: 378, 1949.
2. Merrill, J. P., Levine, H. D., Somerville, W., and Smith, S., III: Clinical recognition and treatment of acute potassium intoxication, Ann. Int. Med. **33**: 797, 1950.
3. Winkler, A. W., Hoff, H. E., and Smith, P. K.: The toxicity of orally administered potassium salts in renal insufficiency, J. Clin. Investigation **20**: 119, 1941.
4. Danowski, T. S.: Newer concepts of the role of potassium in disease, Am. J. Med. **7**: 525, 1949.
5. Darrow, D. C.: Medical progress: body-fluid physiology: the role of potassium in clinical disturbances of body water, and electrolytes, New England J. Med. **242**: 978, 1014, 1950.
6. Elkinton, J. R., and Tarail, R.: The present status of potassium therapy, Am. J. Med. **9**: 200–207, 1950.
7. Fenn, W. O.: The role of potassium in physiological processes, Physiol. Rev. **20**: 377, 1940.

8. Tarail, R.: Relation of abnormalities in concentration of serum potassium to electrocardiographic disturbances, Am. J. Med. **5**: 828–837, 1948.
9. Bills, C. E., McDonald, F. G., Neidermeier, W., and Schwartz, M. C.: Sodium and potassium in foods and waters; determination by the flame photometer, J. Am. Dietet. A. **25**: 304, 1949.
10. Sherman, H. C.: Chemistry of food and nutrition, 1941, The Macmillan Co., New York.
11. Berliner, R. W., and Kennedy, T. J., Jr.: Renal tubular excretion of potassium in the normal dog, Proc. Soc. Exper. Biol. and Med. **67**: 542, 1948.
12. Berliner, R. W.: Renal excretion of water, sodium, chloride, potassium, calcium, and magnesium, Am. J. Med. **9**: 541, 1950.
13. McCance, R. A., and Widdowson, E. M.: Alkalosis with disordered kidney functions: observations on case, Lancet **2**: 247, 1937.
14. Mudge, G. H., Foulks, J., and Gilman, A.: The renal excretion of potassium, Proc. Soc. Exper. Biol. and Med. **67**: 545, 1948.
15. Sirota, J. H., and Kroop, I. G.: Evidence suggesting renal tubular excretion of potassium in man during recovery from acute renal insufficiency, J. Clin. Investigation **30**: 1082–1088, 1951.
16. Elkinton, J. R., and Taffel, M.: Prolonged water deprivation in the dog, J. Clin. Investigation **21**: 787–794, 1942.
17. Tarail, R., and Elkinton, J. R.: Potassium deficiency and the role of the kidney in its production, J. Clin. Investigation **28**: 99, 1949.
18. Borst, J. G. G.: The cause of hyperchloremia and hyperazotemia in patients with recurrent massive hemorrhage from peptic ulcer, Acta med. Scandinav. **97**: 68–88, 1938.
19. Ferrebee, J. W., Ragan, C., Atchley, D. W., and Loeb, R. F.: Desoxycorticosterone esters: certain effects in the treatment of Addison's disease, J. A. M. A. **113**: 1725, 1939.
20. Sartorius, O. W., and Roberts, K.: The effects of Pitressin and desoxycorticosterone in low dosage on the excretion of sodium, potassium and water by the normal dog, Endocrinology **45**: 273, 1949.
21. Fenn, W. O.: Deposition of potassium and phosphate with glycogen in rat livers, J. Biol. Chem. **128**: 297, 1939.
22. Deane, N., and Smith, H. W.: The distribution of sodium and potassium in man, J. Clin. Investigation **31**: 197–199, 1952.
23. Abrams, W. B., Lewis, D. W., and Bellet, S.: The effects of acidosis and alkalosis on the plasma potassium concentration and the electrocardiogram of normal and potassium depleted dogs, Am. J. M. Sc. **222**: 506–515, 1951.
24. Nadler, C. S., Bellet, S., and Lanning, M.: Influence of serum potassium and other electrolytes on the electrocardiogram in diabetic acidosis, Am. J. Med. **5**: 838–848, 1948.
25. Talbot, N. B., Butler, A. M., and MacLachlan, E. A.: Effect of testosterone and allied compounds on mineral, nitrogen and carbohydrate metabolism of a girl with Addison's disease, J. Clin. Investigation **22**: 583–593, 1943.
26. Danowski, T. S., and Elkinton, J. R.: Exchanges of potassium related to organs and systems, Pharmacol. Rev. **3**: 42, 1951.
27. Crismon, J. M., Crismon, C. S., Calabresi, M., and Darrow, D. C.: Electrolyte redistribution in cat heart and skeletal muscle in potassium poisoning, Am. J. Physiol. **139**: 667–674, 1943.
28. Miller, H. C., and Darrow, D. C.: Relation of muscle electrolyte to alterations in serum potassium and to toxic effects of injected potassium chloride, Am. J. Physiol. **130**: 747–758, 1940.
29. Miller, H. C., and Darrow, D. C.: Relation of serum and muscle electrolytes, particularly potassium, to voluntary exercise, Am. J. Physiol. **132**: 801–809, 1941.

30. Arden, F.: Experimental observations upon thirst and on potassium overdosage, Australian J. Exper. Biol. and M. Sc. **12**: 121, 1934.
31. Keith, N. M., and Osterberg, A. E.: The tolerance for potassium in severe renal insufficiency: a study of ten cases, Tr. A. Am. Physicians **59**: 62, 1946.
32. Winkler, A. W., Hoff, H. E., and Smith, P. K.: Electrocardiographic changes and concentration of potassium in serum following intravenous injection of potassium chloride, Am. J. Physiol. **124**: 478, 1938.
33. Bull, G. M., Joekes, A. M., and Lowe, K. G.: Renal function studies in acute tubular necrosis, Clin. Sc. **9**: 379–404, 1950.
34. Stock, R. J.: Acute urinary suppression: observations in twenty-two patients, Am. J. Med. **7**: 45, 1949.
35. Hopper, J., Jr., and Partridge, J. W.: Anuria and oliguria: a review of symptoms, pathologic physiology and mortality rates, California Med. **72**: 415, 1950. Ibid: Anuria and oliguria: treatment by conservative means, case report, with determination of blood volume and Na_{as} space, California Med. **73**: 42–53, 1950.
36. Hald, P. M.: The flame photometer for the measurement of sodium and potassium in biological materials, J. Biol. Chem. **167**: 499, 1947.
37. Kramer, P., and Tisdall, F. F.: A simple technique for the determination of calcium and magnesium in small amounts of serum, J. Biol. Chem. **47**: 475, 1921.
38. Shinowara, G. Y., Jones, L. M., and Reinhart, H. L.: The estimation of serum inorganic phosphate and "acid" and "alkaline" phosphatase activity, J. Biol. Chem. **142**: 921, 1942.
39. Van Slyke, D. D., and Hiller, A.: Application of Sendroy's idometric chloride titration to protein-containing fluids, J. Biol. Chem. **167**: 107–124, 1947.
40. Peters, J. P., and Van Slyke, D. D.: Quantitative clinical chemistry. Vol. II. Methods, 1932, Williams & Wilkins Co., Baltimore.
41. Borst, J. G. G.: Protein katabolism in uremia: effects of protein free diet, infections, and blood transfusions, Lancet **1**: 824–828, 1948.
42. Bull, G. M., Joekes, A. M., and Lowe, K. G.: Conservative treatment of anuric uremia, Lancet **2**: 229–234, 1949.
43. Elkinton, J. R., Clark, J. K., Squires, R. D., Bluemle, L. W., Jr., and Crosley, A. P., Jr.: Treatment of potassium retention in anuria with cation exchange resin: a preliminary report, Am. J. M. Sc. **220**: 547, 1950.
44. Welt, L. G., and Peters, J. P.: Acute renal failure: lower nephron nephrosis, Yale J. Biol. and Med. **24**: 220, 1951.
45. Bradley, S. E.: The pathologic physiology of uremia in chronic Bright's disease, 1948, Charles C. Thomas, Springfield.
46. Aggeler, P., and Lucia, S. P.: Hemorrhagic disorders, 1949, University of Chicago Press, Chicago.
47. Levine, H. D., Vazifdar, J. P., Lown, B., and Merrill, J. P.: "Tent-shaped" T waves of normal amplitude in potassium intoxication, Am. Heart J. **43**: 437, 1952.
48. Aitken, R. S., Allott, E. N., Castleden, L. I. M., and Walker, M.: Observations on a case of familial periodic paralysis, Clin. Sc. **3**: 47, 1937.
49. Harrop, G. A., Jr., and Benedict, E. M.: The participation of inorganic substances in carbohydrate metabolism, J. Biol. Chem. **59**: 683, 1924.
50. Kerr, S. E.: Effect of insulin and of pancreatotomy on distribution of phosphorus and potassium in blood, J. Biol. Chem. **78**: 35, 1928.
51. Seldin, D. W., and Tarail, R.: Effect of hypertonic solutions on metabolism and excretion of electrolytes, Am. J. Physiol. **159**: 160–174, 1949.
52. Tarail, R., Seldin, D. W., and Goodyear, A. V. N.: Effects of injection of hypertonic glucose on metabolism of water and electrolytes in patients with edema, J. Clin. Investigation **30**: 1111–1119, 1951.

53. Hald, P. M., Tulin, M., Danowski, T. S., Lavietes, P. H., and Peters, J. P.: Distribution of sodium and potassium in oxygenated human blood and their effects upon movement of water between cells and plasma, Am. J. Physiol. **149**: 340–349, 1947.
54. Govan, C. D., Jr., and Weiseth, W. M.: Potassium intoxication: report of an infant surviving a serum potassium level of 12.27 millimoles per liter, J. Pediat. **28**: 550, 1946.
55. Currens, J. H., and Crawford, J. D.: The electrocardiogram and disturbance of potassium metabolism, New England J. Med. **243**: 843, 1950.
56. Ringer, S.: Concerning influence exerted by each of constituents of blood on contraction of ventricle, J. Physiol. **3**: 380–393, 1882.
57. Ringer, S.: Further contribution regarding influence of different constituents of blood on contraction of heart, J. Physiol. **4**: 29–42, 1883.
58. Govan, C. D., Jr., and Darrow, D. C.: The use of potassium chloride in the treatment of the dehydration of diarrhea in infants, J. Pediat. **28**: 541, 1946.
59. Marchand, J. F., and Finch, C. A.: Fatal spontaneous potassium intoxication in patients with uremia, Arch. Int. Med. **73**: 384, 1944.
60. Salter, W. T., and Runels, E. A.: A nomogram for cardiac contractility involving calcium, potassium, and digitalis-like drugs, Am. J. Physiol. **165**: 520–526, 1951.
61. Cohen, B. M.: Digitalis poisoning and its treatment, New England J. Med. **246**: 254, 1952.
62. Payne, F. E., Bennett, L. L., Burstein, S. G., and Hopper, J., Jr.: Manifestations of potassium intoxication in the dog heart-lung preparation, Federation Proc. **8**: 125, 1949.
63. Castleden, L. I. M.: The effect of potassium salts on cardiac irregularities, Brit. M. J. **1**: 7–9, 1941.
64. Sampson, J. J., Alberton, E. C., and Kondo, B.: Effect on man of potassium administration in relation to digitalis glycosides, with special reference to blood serum potassium, electrocardiogram, and ectopic beats, Am. Heart J. **26**: 164–179, 1943.
65. Sampson, J. J., and Anderson, E. M.: Therapeutic use of potassium in certain cardiac arrhythmias, Proc. Soc. Exper. Biol. and Med. **28**: 163–165, 1930.
66. Zwemer, R. L., and Lowenstein, B. E.: Cortin-like effects of steroid glycosides on potassium, Science **91**: 75, 1940.
67. Burstein, S. G., Bennett, L. L., Payne, F. E., and Hopper, J., Jr.: Effects of potassium and lanatoside-C on the failing heart in heart-lung preparations, Federation Proc. **8**: 20, 1949.
68. Lown, B., Salzberg, H., Enselberg, C. D., and Weston, R. E.: Interrelations between potassium metabolism and digitalis toxicity in heart failure, Proc. Soc. Exper. Biol. and Med. **76**: 797, 1951.
69. Lown, B., Weller, J., Merrill, J. P., and Criscitello, M.: Digitalis toxicity induced by the depletion of potassium through hemodialysis. In preparation. Cited by Levine, H. D., Vazifdar, J. P., Lown, B., and Merrill, J. P.[47]

A LONG-TERM EVALUATION OF AUREOMYCIN IN THE TREATMENT OF ACTINOMYCOSIS*

By Leon V. McVay, Jr., M.D., and Douglas H. Sprunt, M.D., F.A.C.P.,
Memphis, Tennessee

With the conquest of one infectious disease entity after another, attention has tended to concentrate on those conditions which have remained resistant to modern methods of therapy. Paramount among these diseases are those caused by the pathogenic fungi. No sphere in clinical research is more active than that concerned with the development of effective modes of treatment for such serious conditions as disseminated histoplasmosis, generalized coccidioidomycosis, cryptococcic meningitis, systemic North American blastomycosis and generalized actinomycosis.

As interest in mycotic infections has grown they are being recognized more frequently. An excellent example is the increased number of cases of systemic North American blastomycosis reported in the past few years.[1-10] While there has been definite progress in the treatment of fungal diseases, many are still classified as fatal.[11]

One of the most dangerous human mycotic infections is actinomycosis, first recognized in 1878.[12] This condition is caused by a specific organism, *Actinomyces bovis*. This pathogenic fungus is a nonspore-forming, strictly anaerobic, gram-positive, branching filamentous organism. It is also the causative agent of lumpy jaw in cattle. After years of disagreement, it has been established that this fungus is strictly parasitic and does not occur outside of the body.[13, 14] Human actinomycosis is, therefore, an endogenous infection. *A. bovis* has been isolated in the apparent absence of disease from the crypts of tonsils, the tartar of teeth, carious teeth, salivary calculi and healthy gums.[15] As the result of trauma, infection, surgery, aspiration of infected material and other causes, this organism may invade the tissues of the body. When this occurs, a nonspecific granulomatous reaction with limited suppuration results. Multiple interconnected abscesses may be formed which may rupture to the surface and produce draining sinuses. In addition to direct extension, invasion of the blood stream may occur with generalized dissemination. Although the exact incidence of actinomycosis is not known, it is far from rare. The first monograph on the subject in the English language did not appear until 1938,[16] and only 700 cases had been reported in the United States by 1922.[15] However, Cope was able to review 1,330 cases in 1938.[16] Since that date progressively larger numbers have been reported each year. Ten patients with this infection have been

* Received for publication December 27, 1952.
From the Departments of Medicine, Pathology and Bacteriology, University of Tennessee College of Medicine, and the John Gaston Hospital, Memphis, Tennessee.

observed at the John Gaston Hospital and the University of Tennessee College of Medicine during the past three years.

From a clinical point of view, actinomycosis may be divided into three types: cervicofacial, thoracic and abdominal. Treatment and prognosis are largely determined by the type of infection.

Innumerable agents have been employed in the treatment of actinomycosis, but only a few have proved of lasting value. Irradiation therapy [17] has been shown to be effective in circumscribed lesions, and the use of appropriate surgical procedures is likewise well established.[18] However, it was not until the advent of the sulfonamides [19] and penicillin [20] that the prognosis of this condition was significantly improved. Even with the advent of these agents, the mortality and morbidity of this infection remained significant. The prognosis is best in cervicofacial actinomycosis, for the mycotic disease is then limited to the tissues of the face, jaw and neck. It must be emphasized, however, that invasion of the blood stream may occur even in this form of actinomycosis (case 2, below). Numerous patients having this type of the disease have been successfully treated by the prolonged administration of sulfadiazine alone or in combination with penicillin.[21-23] Where the lung is involved, therapy is difficult. In 1946 Kay reported two cases of pulmonic actinomycosis treated intensively with sulfadiazine and penicillin alone and in combination almost continuously for a year, but pneumonectomy was finally required in both cases.[24] However, several patients suffering from pulmonic involvement have responded to intensive and extended therapy with penicillin.[25, 26] Kolouch and Peltier [17] reviewed 330 cases of abdominal actinomycosis in 1946 and reported 30 per cent cured, 10 per cent improved, 54 per cent dead and 6 per cent not followed. Sixteen of these patients had been treated with sulfonamides, with the following results: 56 per cent cured, 18 per cent improved, 18 per cent dead and 4 per cent not followed. In 1949 Sanford and Barnes [27] surveyed the literature and reported 19 cases of abdominal actinomycosis treated with penicillin. The mortality rate in this group was 15.8 per cent.

Believing that further improvement in the treatment of actinomycosis was essential, in 1949 we began a study of the effectiveness of aureomycin in this mycotic disease. In vitro sensitivity studies, using four strains of *A. bovis*, established a definite inhibitory effect by this antibiotic.[28] Subsequently, this antagonistic action was demonstrated with three additional strains.

Excellent initial clinical results were obtained using aureomycin in human actinomycosis.[28, 29] However, it was emphasized that prolonged observation was necessary to evaluate accurately the efficiency of this method of treatment. That fungal infections are chronic and prone to recurrence is well recognized. Indeed, this appears to be a major explanation of an all too frequent phenomenon in the literature dealing with the treatment of fungus diseases: innumerable agents are reported as being effective and are

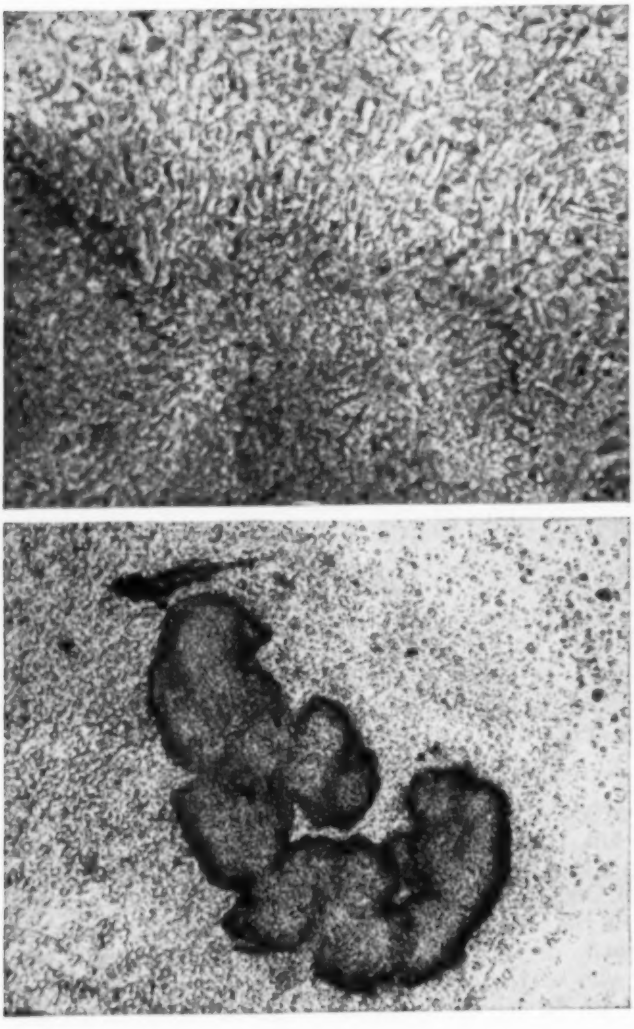
then never heard of again. In chronic diseases, prolonged and careful observation is essential to the ultimate evaluation of any method of treatment. Encouraging initial results are not sufficient.

Five cases of actinomycosis treated with aureomycin have been followed for more than two years since the completion of therapy. In no instance has any evidence of recurrence been observed. In three of these patients who had localized cervicofacial actinomycosis, the follow-up periods are 36, 33 and 32 months, respectively. Another patient had a hepatic abscess caused by *A. bovis* and *Bacteroides funduliformis*. After a critical illness requiring 70 days of hospitalization, an excellent response to treatment occurred. The observation period in this instance is 30 months since treat-

A B

FIG. 1A. *Case 1*, lesion of cervicofacial actinomycosis before treatment. B. ***Case 1***, six months following therapy.

ment. The fifth patient had cervicofacial involvement. The follow-up period in this last case is 25 months since the completion of therapy. The three cases of localized cervicofacial actinomycosis followed the extraction of teeth, but in the remaining two instances, the initiating factor was not clear. Two and one-half years after treatment, the patient who had been critically ill with hepatic actinomycosis is entirely asymptomatic, works regularly and has maintained his normal weight for more than two years. Although in this case it was necessary to aspirate the liver nine times, not even abdominal induration can now be palpated. Serial hematologic examinations have remained normal. An additional instance of localized actinomycosis following trauma to the head in an automobile accident was successfully treated with aureomycin and has been observed for six months



B

A

FIG. 2A. *Case 1*, showing a sulfur-like granule in a moist preparation (low power magnification). B. *Case 1*, peripheral portion of the granule under high power magnification, showing the typical club-shaped appearance of the ends of the filaments.

without evidence of recurrence. A seventh case of cervicofacial actinomycosis which gave rise to generalized infection and hemorrhagic nephritis is reported below (case 2).

Case Reports

Case 1. A 55 year old Negro female was hospitalized on September 19, 1950, because of painless swelling in the region of the right jaw. Approximately six weeks prior to entry into the hospital the patient had noted rather severe pain over the inferior and lateral aspects of the right mandible. A private physician was consulted who administered 600,000 units of penicillin intramuscularly initially and, thereafter, 1 gm. of sulfadiazine orally every four hours for a week. Subsequently no significant discomfort was noted. However, an area of painless induration developed which became progressively larger. On September 12 the patient was observed at the West

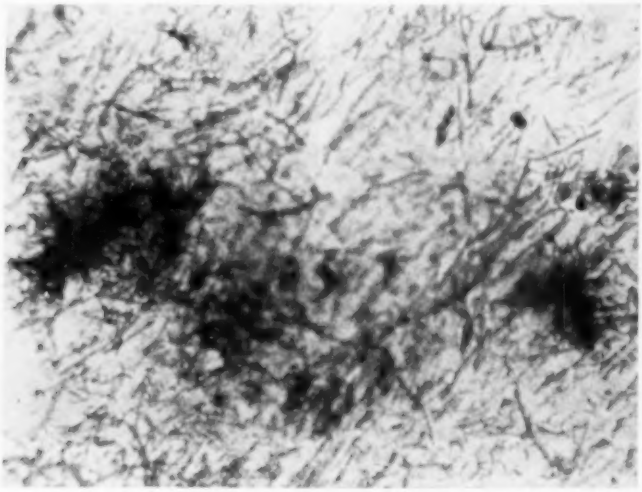


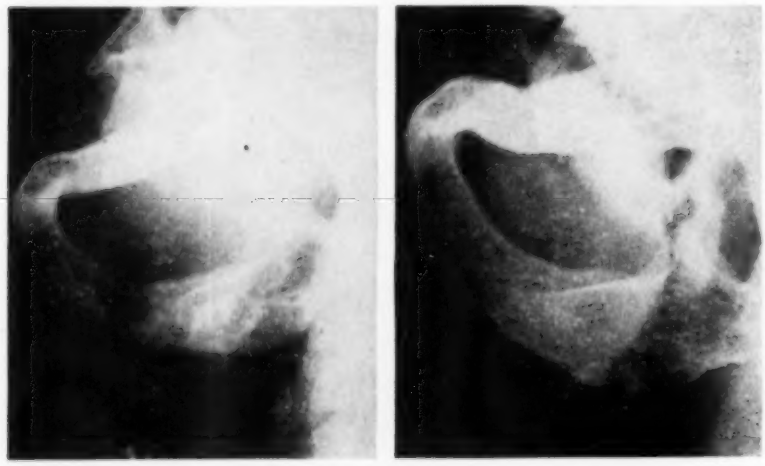
Fig. 3. *Case 1*, a sulfur-like granule crushed and stained to show branching, gram-positive filaments.

Tennessee Cancer Clinic and was referred to the University of Tennessee Dental Clinic. From the latter she was sent on consultation to the Antibiotic Clinic of the John Gaston Hospital. A review of the case disclosed no history of trauma and no contact with tuberculosis. There had been no weight loss. The clinical picture was believed to be that of cervicofacial actinomycosis, and the patient was admitted to the Medical Service of the John Gaston Hospital.

Examination upon hospitalization revealed the temperature to be 99° F., pulse 78, respirations 24, and blood pressure 160 mm. of Hg systolic and 100 mm. diastolic. An erythematous area measuring 5 by 4 cm. was located over the lateral and inferior portion of the right mandible (figure 1A). This lesion was nontender to palpation and was woody in consistency except for a small fluctuant central portion. The anterior teeth could be separated 3.5 cm.

After the involved area had been prepared with iodine and alcohol the fluctuant area was aspirated. Approximately 2 c.c. of yellowish, purulent material were obtained. A moist preparation disclosed the characteristic sulfur-like granules of *A. bovis* (figures 2A and 2B). Crushing and staining a granule disclosed the characteristic gram-positive, branching organism (figure 3). Subsequently the diagnosis was confirmed by culture. A roentgenogram of the right mandible was interpreted as revealing osteomyelitis in the horizontal ramus, with associated soft tissue swelling; the possibility of malignancy was suggested (figure 4A). On September 28 aureomycin treatment was begun; 750 mg. were administered four times a day for two weeks, and thereafter, medication was reduced to 2 gm. daily for three weeks. In this manner a total of 84 gm. was administered during a period of five weeks.

Progressive clinical improvement was observed. After two weeks the lesion had decreased to 2.8 by 2.8 cm. in size and the anterior teeth could be separated 4.3 cm. The patient was discharged on November 6, 1950, to be observed at semimonthly



A B

FIG. 4A. *Case 1*, roentgenogram of the right mandible before treatment. B. *Case 1*, roentgenogram obtained on November 29, 1951.

intervals through the Antibiotic Clinic. When the patient left the hospital, only scarification marked the site of the previous lesion.

A roentgenogram of the right mandible was obtained every two months, with definite improvement first observed on March 8, 1951. Thereafter, restoration of the bony architecture was continuously progressive until on November 29, 1951, no evidence of any lesion could be demonstrated roentgenologically (figure 4B). Physical examination was nonrevealing six months after treatment (figure 1B). This patient has been observed at regular intervals with no evidence of recurrence of infection.

Laboratory Findings: The admission white blood cell count was 9,400 with the polymorphonuclear leukocytes 31 per cent, lymphocytes 63 per cent, monocytes 4 per cent, basophils 1 per cent and eosinophils 1 per cent. The red blood cell count was 4,200,000, with a hemoglobin of 12 gm. and a hematocrit of 36 ml. per cent. An initial urinalysis was within normal limits.

Case 2. A 60 year old Negro male was admitted to the General Surgery Service

of John Gaston Hospital on August 12, 1952. Approximately 10 weeks prior to hospitalization this patient had noted a painless indurated nodule on the left lateral aspect of the neck about 2 cm. inferior to the angle of the jaw. From this period until hospitalization innumerable similar lesions appeared over the entire body, except on the soles and palms. The development of these lesions was described as follows: painless induration with reddish discoloration and associated slight tenderness was initially observed; in about 50 to 60 per cent of cases this was followed by the development of a small fluctuant area which eventually ruptured and gave rise to a minimal amount of sanguinopurulent material. Drainage was odorless. Apparently 40 to 50 per cent of the lesions remained in the indurated stage and did not progress to suppuration. Approximately six weeks before admission to the hospital a large indurated area appeared in the right posterior axillary line which eventually became fluctuant and formed a chronic ulcer. Initially, a small amount of thin, odorless, sero-

A B

FIG. 5A. *Case 2*, actinomycotic lesions before aureomycin treatment. B. *Case 2*, lesions after therapy.

sanguineous material was described as draining from this lesion, but subsequently, this became thick, greenish and foul smelling. Until one week prior to entry into the hospital, this large lesion remained essentially painless. Thereafter, it produced moderate discomfort, but the patient could still sleep on his right side and back.

Anorexia, night sweats, malaise, exertional dyspnea, palpitation, weakness and dizziness became progressively severe. A 46 pound weight loss occurred during this period. Complete bed-rest had been required for four weeks.

Examination upon hospitalization revealed a temperature of 98° F., pulse 110, respirations 28, and blood pressure 190 mm. of Hg systolic and 110 mm. diastolic. With the exception of the palms and soles, the body was largely covered with several hundred lesions (figure 5A). Approximately 50 per cent were indurated, woody in consistency, reddish brown in color, and essentially nontender; and approximately 35 per cent revealed a small area of fluctuation on palpation, though they were only slightly tender. The remaining cutaneous lesions (approximately 15 per cent) had

formed chronic ulcers. The largest ulceration was located in the right middle and posterior axillary line at the level of the tip of the scapula. This lesion measured 8 by 7 cm. in size and disclosed a necrotic base covered by thick, greenish yellow, foul smelling exudate. All mucous membranes were extremely pale. Aside from a tachycardia of 110 per minute, the thoracic examination was within normal limits.

The clinical impression was generalized furunculosis with one large carbuncle. Therapy consisted of 300,000 units of aqueous penicillin intramuscularly every three hours; likewise, 1 gm. of dihydrostreptomycin was administered intramuscularly initially, and then 0.5 gm. every 12 hours. Continuous warm saline compresses were applied to the draining lesions. Because of the hypertension, a low sodium diet was employed. The admission urinalysis disclosed 50 to 70 red blood cells per high power field of a centrifuged specimen. Three days later no clinical improvement was evident, and nausea, vomiting and grossly bloody urine had developed. The blood nonprotein nitrogen was 149 mg. per cent. The patient was therefore transferred to the Medical Service.

Immediately upon admission to the Medical Service three widely separated and nondraining lesions were aspirated, using aseptic technic. These yielded a minute amount of thick, yellow, mucopurulent material. A moist preparation in every instance disclosed sulfur-like granules, the diagnosis of actinomycosis being subsequently confirmed by microscopic and cultural studies. *Micrococcus pyogenes* var. *aureus* was likewise demonstrated. Aureomycin therapy was instituted, using 500 mg. intravenously in 500 c.c. of 5 per cent glucose in distilled water every eight hours, streptomycin was continued for four days, and penicillin for 10 days. After a week aureomycin was reduced to 500 mg. intravenously every 12 hours, and five days later was further reduced to 250 mg. intravenously every 12 hours. Intravenous medication was discontinued on September 22. Thereafter, 250 mg. of aureomycin were administered every four hours until the patient was discharged from the hospital.

Because of vomiting the patient had to be maintained almost entirely on parenteral fluids for 18 days. During this period he received eight blood transfusions of 500 c.c. each. Thereafter, persistent nausea without vomiting was present. A Levine tube was passed and the patient was placed on a daily diet consisting of 30 gm. of protein, 225 gm. of carbohydrate and 100 gm. of fat in 3,000 c.c. of water. Salt was omitted. In addition, 1,000 c.c. of 5 per cent glucose in distilled water were administered intravenously each day. The latter contained vitamin supplements. One cubic centimeter of crude liver was injected intramuscularly every other day.

Tube feeding was discontinued on September 10. Thereafter, the low protein diet was continued and fluids were forced by mouth. The intravenous administration of 5 per cent glucose and vitamin supplements once daily was continued for an additional 10 days. After September 16, the patient had a voracious appetite.

On this therapeutic regimen the cutaneous lesions displayed rapid improvement. A mixture of streptokinase and streptodornase with aureomycin powder was applied locally to the largest ulceration. This preparation had previously been found to be effective in chronic ulcers.[29, 30] Azotemia and anemia responded slowly. Gross hematuria disappeared about September 20, and only occasional red blood cells were observed in the urine after September 29. On October 25 the patient was discharged, to be observed at weekly intervals through the Antibiotic Clinic.

Nine weeks after leaving the hospital the patient was entirely asymptomatic except for weakness, which was progressively decreasing. There had been a gain of 14 pounds in weight since the completion of treatment.

Laboratory Findings: The red blood cell count ranged from 1,740,000 to 4,240,000; the hemoglobin from 6 to 12.5 gm.; the hematocrit from 23 to 38 ml. per cent; the white blood cell count from 5,650 to 15,500 per cubic millimeter; the blood non-

protein nitrogen from 54 to 216 mg. per cent; plasma creatinine from 3.6 to 14.6 mg. per cent; plasma carbon dioxide combining power from 6 to 21 mEq./L.: total plasma protein from 6.0 to 7.4 gm. per cent, with albumin 3.5 to 4.2 gm. per cent and globulin from 2.5 to 3.2 gm. per cent; cephalin cholesterol flocculation determinations from 2 plus to 0 at 24 hours; an initial total serum bilirubin was 0.2 mg. per cent; blood calcium from 8.5 to 10.5 mg. per cent; plasma sodium from 150 to 130 mEq./L.; plasma potassium from 3.1 to 4.6 mEq./L.: plasma chlorides from 114.4 to 117.7 mEq./L. Multiple urinalyses revealed a pH from 4.5 to 6.0; specific gravity from 1.008 to 1.012; proteinuria from 3 plus to 0; red blood cells per high power field (centrifuged) too numerous to count (gross blood) to 0; white blood cells per high power field (centrifuged) 3 to 5 up to 30 to 50 with clumping. An initial urine culture was positive for *Escherichia coli* and *Streptococcus faecalis*. Six blood cultures were negative. The blood Kahn test was negative. A bone marrow culture was negative for fungi.

Discussion

The treatment of fungal diseases is becoming an increasingly important medical problem, inasmuch as these infections are being recognized much more frequently than in the past. While many factors are doubtless involved in this development, a few of the more important are probably included in the following: the effective treatment and virtual elimination of many more common infectious diseases, a greater interest in mycotic infections in medical schools and in the current literature and, finally, the more general availability of inexpensive laboratory facilities. Whatever the exact reasons, the pathogenic fungi are being considered much more frequently in differential diagnoses.

Actinomycosis should be considered in the differential diagnosis of all subacute and chronic infectious processes. This is especially true if the cervicofacial area is involved and if there is a previous history of trauma. While this mycotic disease is most dangerous in its disseminated, neurogenic, thoracic and abdominal forms, it must be emphasized that even the localized type may cause blood stream infection. This was illustrated in case 2 in the present paper. The development of effective therapeutic measures in actinomycosis, as in most fungal infections, has tended to lag behind advances in diagnosis. The value of irradiation treatment in the localized type of the disease is well recognized,[17] and surgical drainage and excision in selected cases are definitely indicated.[18] However, the prolonged administration of sulfadiazine and penicillin alone and in combination afforded the greatest improvement in the prognosis of this disease.[19-27] This was especially true in the thoracic and abdominal forms. Nevertheless, the mortality and morbidity of actinomycosis remained significant.

Therefore, the fact that aureomycin is effective against *A. bovis* in vitro and in vivo is of great importance. Five cases treated with aureomycin have been followed for more than two years, with no evidence of recurrence. Included in this group are three cases of localized cervicofacial actinomycosis which were followed for 36, 33 and 32 months, respectively, after treatment.

An additional patient having cervicofacial involvement with direct extension into the mandible has been observed for 32 months. One case of hepatic actinomycosis has been carefully followed for 30 months. No evidence of infection is present in any of these cases as indicated by careful questioning, examination, and laboratory and roentgenologic studies. Two additional cases have been observed for two and six months since therapy, with no evidence of recurrence of disease.

It appears that 750 mg. of aureomycin administered orally every six hours for 10 days and thereafter 500 mg. every six hours for 18 days are usually effective in cervicofacial actinomycosis. With involvement of bone, a greater amount may be required. After 84 gm., all evidence of osseous involvement disappeared in one patient. That aureomycin is effective in abdominal actinomycosis has recently been confirmed elsewhere.[31] In this severe form of the disease, prolonged treatment using the intravenous form of administration may be required. Supportive therapy in such cases should include the maintenance of nutrition as well as fluid and electrolyte balance. This often entails the use of blood transfusions, parenteral administration of fluids and vitamin supplements. Two and one-half years following treatment, there is no evidence of infection in a patient who had had proved hepatic actinomycosis. Not even induration can be palpated at the sites of repeated aspiration.

Aureomycin may not be effective in all cases of actinomycosis. One patient with a cervicofacial form of this disease has been followed for two and one-half years. In this instance, temporary improvement with subsequent recurrence has followed therapeutic courses of aureomycin, penicillin and sulfadiazine, pentamidine and stilbamidine. The failure of response to stilbamidine is of interest in view of its recently reported effectiveness in one case.[32]

It is the opinion of the authors that an observation period of five years following treatment may be necessary to establish definitely the cure of systemic or visceral actinomycosis. Nevertheless, on the basis of the present studies it appears that aureomycin is an effective agent for the treatment of this disease.

Summary

1. Actinomycosis is being diagnosed with increasing frequency. Ten cases have been observed at the John Gaston Hospital and the University of Tennessee College of Medicine during the past three years.

2. Actinomycosis should be considered in the differential diagnosis of all subacute and chronic inflammatory processes in which the etiologic agent is not readily obvious. This is especially true if the cervicofacial region is involved and if a history of trauma is elicited.

3. Aureomycin exerts a definite inhibitory effect on *Actinomyces bovis* in vitro.

4. Seven cases of actinomycosis have been successfully treated with aureomycin, five of which have been observed for more than two years since treatment.

5. Aureomycin is an effective therapeutic agent in localized and disseminated actinomycosis.

ACKNOWLEDGMENT

The authors wish to express their sincere appreciation to Conley H. Sanford, M.D., F.A.C.P., for his invaluable assistance in this study.

BIBLIOGRAPHY

1. Friedman, L. L., and Signorelli, J. J.: Blastomycosis: a review of the literature and a report of a case involving the meninges, Ann. Int. Med. **24**: 385–400 (March) 1946.
2. Littman, M. L., Wicker, E. H., and Warren, A. S.: Systemic North American blastomycosis. Report of a case with cultural studies of the etiologic agent and observations on the effect of streptomycin and penicillin in vitro, Am. J. Path. **24**: 339–365 (March) 1948.
3. Smith, D. T.: Immunologic types of blastomycosis: a report of 40 cases, Ann. Int. Med. **31**: 463–469, 1949.
4. Benham, R. W.: Cryptococcosis and blastomycosis, Ann. New York Acad. Sc. **50**: 1299, 1950.
5. Schoenbach, E. B., Miller, J. M., Ginsberg, M., and Long, P. H.: Systemic blastomycosis treated with stilbamidine, J. A. M. A. **146**: 1317–1318 (Aug. 4) 1951.
6. Noojin, R. O., and Praytor, H. B.: Systemic blastomycosis complicated with pregnancy, J. A. M. A. **147**: 749–751 (Oct. 20) 1951.
7. Schwartz, J., and Baum, G. L.: Blastomycosis, Am. J. Clin. Path. **21**: 999–1100 (Nov.) 1951.
8. McVay, L. V., Jr., and Carroll, D. S.: Aureomycin in the treatment of systemic North American blastomycosis, Am. J. Med. **12**: 289–301 (March) 1952.
9. Schoenbach, E. B., Miller, J. M., and Long, P. H.: Treatment of systemic blastomycosis with stilbamidine, Ann. Int. Med. **37**: 31–47 (July) 1952.
10. Snapper, I., Schneid, B., McVay, L., and Lieben, F.: Pharmacology and therapeutic value of diamidine derivatives—particularly of 2-hydroxystilbamidine, Tr. New York Acad. Sc. **14**: 269–271 (May) 1952.
11. Martin, D. S.: Fungous diseases involving the internal organs, *in* Harrison, T. R.: Principles of internal medicine, 1951, Blakiston and Co., Philadelphia, pp. 941–955.
12. Israel, J.: Neue Beobachtungen auf dem Gebiete der Mykosen des Menschen, Arch. f. path. Anat. **74**: 15–53, 1878.
13. Wolff, M., and Israel, J.: Über Reinculture des Actinomyces und seine Übertragbarkeit auf Thiere, Arch. f. path. Anat. **126**: 11–59, 1891.
14. Wright, J. H.: Biology of micro-organisms of actinomycosis, J. M. Research **13**: 349–404, 1905.
15. Davis, M. I. J.: Analysis of forty-six cases of actinomycosis with special reference to its etiology, Am. J. Surg. **52**: 447–454, 1941.
16. Cope, Z.: Actinomycosis, 1938, Oxford University Press, London.
17. Kolouch, F., and Peltier, L. F.: Recent advances in surgery: actinomycosis, Surgery **20**: 401–430, 1946.
18. Wangensteen, O. H.: The role of surgery in the treatment of actinomycosis, Ann. Surg. **104**: 752–770, 1936.
19. Poulton, E. P.: Discussion of the treatment of bacterial diseases with substances related to sulphanilamide, Proc. Roy. Soc. Med. **31**: 149–166, 1938.

20. Florey, M. E., and Florey, H. W.: General and local administration of penicillin, Lancet **1**: 387–396, 1943.
21. Dobson, L., and Cutting, W. C.: Penicillin and sulfonamides in the therapy of actinomycosis: report of 16 additional cases and in vitro tests of susceptibility of actinomyces to penicillin and sulfadiazine, J. A. M. A. **128**: 856–863, 1945.
22. Walker, J. M., and Hamilton, J. W.: Treatment of actinomycosis with penicillin, Ann. Surg. **121**: 373–384, 1945.
23. Hendrickson, G. G., and Lehman, E. P.: Cervicofacial actinomycosis successfully treated by penicillin without surgical drainage, J. A. M. A. **128**: 438, 1945.
24. Kay, E. B.: Pulmonary actinomycosis: its treatment by pulmonary resection in conjunction with chemotherapy: report of two cases, Ann. Surg. **124**: 535–543, 1946.
25. Roberts, J. E. H., Tubbs, O. S., and Bates, M.: Pleural and pulmonary suppuration treated with penicillin, Lancet **1**: 39–45, 1945.
26. Nichols, D. R., and Herrell, W. E.: Penicillin in treatment of actinomycosis, J. Lab. and Clin. Med. **32**: 1405, 1947.
27. Sanford, G. E., and Barnes, R. O.: Massive penicillin therapy of abdominal actinomycosis, Surgery **25**: 711–723, 1949.
28. McVay, L. V., Jr., Guthrie, F., and Sprunt, D. H.: Aureomycin in the treatment of actinomycosis, New England J. Med. **245**: 91–96 (July 19) 1951.
29. McVay, L. V., Jr., Dunavant, D., Guthrie, F., and Sprunt, D. H.: Treatment of actinomycosis with aureomycin, J. A. M. A. **143**: 1067–1068 (July 22) 1950.
30. McVay, L. V., Jr., and Sprunt, D. H.: Streptokinase and streptodornase in the treatment of diabetic gangrene, Arch. Int. Med. **87**: 551–559 (April) 1951.
31. Berg, J. A. G.: Personal communication, Dutch M. J. (Nov. 8) 1952.
32. Miller, J. M., Long, P. H., and Schoenbach, E. B.: Successful treatment of actinomycosis with stilbamidine, J. A. M. A. **150**: 35 (Sept. 6) 1952.

DEVELOPMENTAL BRONCHIAL CYSTS *

By S. G. Baxter, M.D., C.M., M.Sc., Ph.D., and J. F. Meakins, M.A., M.D., C.M., F.R.C.P.(C), F.A.C.P., F.C.C.P.,
Montreal, Canada

The problem of congenital or developmental bronchial and pulmonary cysts has occupied the interest of roentgenologists, chest physicians and surgeons since the writings of Koontz [1] in 1925 and later Schenck.[2] During the past quarter-century a voluminous literature on the subject has been published. It is with some diffidence that we add our small series, but we believe it will be of interest.

Within the broad term of pulmonary cystic disease many entities have been included, many names used, and many classifications presented based on origin, site, mechanism of formation and pathology.[2-10] We prefer the simple classification proposed by Cooke and Blades [3] (table 1), as it meets all reasonable demands and eliminates numerous pseudocystic disease entities. Most authors [3, 7, 8, 11] agree with Strode [10] in his brief, clear outline of the tissue makeup of the two main types of cysts: "Bronchiogenic cysts are characterized by their walls being made up of elements of the bronchus—namely, cartilage, smooth muscle, elastic tissue, and mucous glands—and are lined by cuboidal or columnar epithelium which may or may not be ciliated. These cysts may contain fluid, pus, blood or air alone or in combination. Alveolar cysts, on the other hand, do not possess an epithelial lining but are lined by alveolar cells that are compressed together to form the wall and they always contain air." In the classification in table 1 there is the third type, with combined or mixed tissue elements. In this presentation we are interested mainly in developmental cysts of bronchial origin.

The question of pathogenesis still remains somewhat confused. The differences of opinion of those favoring congenital origin on the one hand, or acquired origin on the other, can be reconciled by the review of the whole problem by Mayer and Rappaport.[4] They demonstrate theoretically and practically that a developmental defect or bronchopulmonary rest may remain a "congenital cyst" or, by extrinsic influences, demonstrate itself and become of such a nature as to be thought "acquired." However, they tend to place all pulmonary disease other than that of very specific etiology or of malignant change under one canopy of combined causes, which seems an oversimplification and with which we do not fully agree. In the problem of "congenital" or "developmental" cysts, and we prefer with Mayer and Rappaport [4] and Peirce [6] the term developmental, the embryology and prenatal and postnatal

* Read at the Annual Meeting of the Royal College of Physicians and Surgeons of Canada, Toronto, October, 1952. Received for publication December 6, 1952.

From the Departments of Medicine and Surgery of the Royal Victoria Hospital, Montreal.

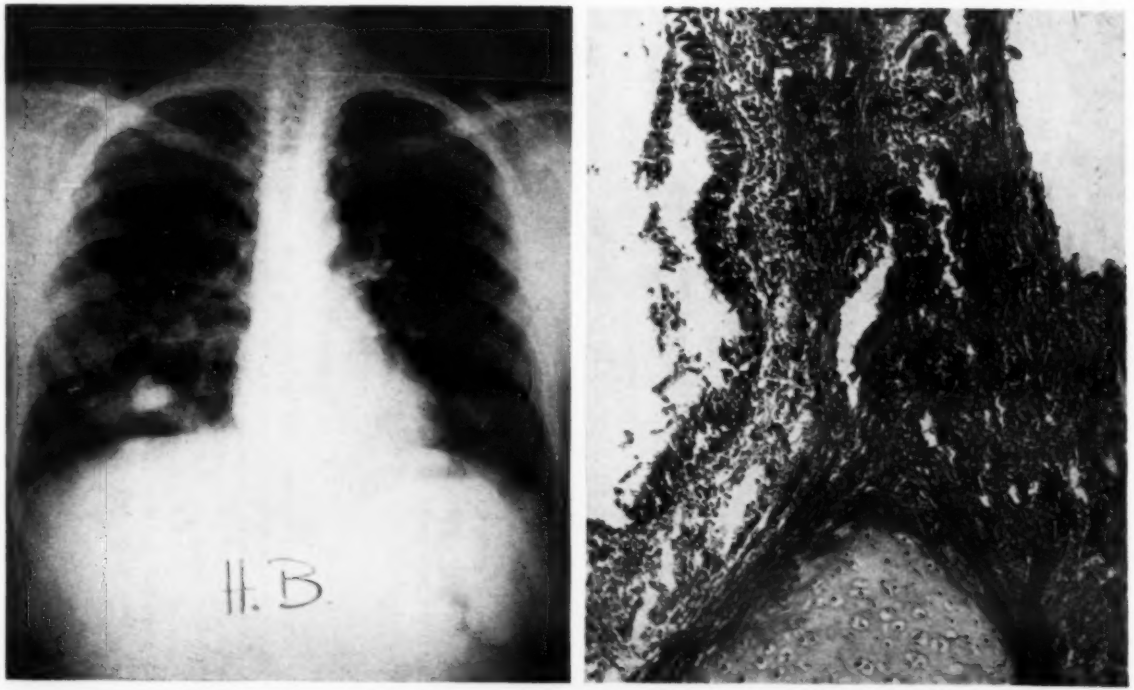
development of the bronchopulmonary tree are of paramount importance. Schenck [2] and Mayer and Rappaport [4] refer to and quote the basic work done by Broman, Willson, Bremer and Engel. In brief, at the end of the fourth embryonic week the hollow evagination called the pulmonary groove appears on the esophageal portion of the primitive gut. From the hind end of this groove there develops an outpouching which, by organized budding division, forms the entire pulmonary system. It is maintained, and proof is presented to establish the fact, that postnatally this process of developmental growth of new bronchopulmonary elements continues until the seventh or eighth year or, in some instances, to as late as the fourteenth year. At any time during this period of development there could come about the anomaly of development leading to "cystic disease" in the bronchopulmonary tree. Peirce [5, 6] supports this in his feeling that such a lesion (cyst or pneumatocele) need not be present from birth but could appear up to the cessation of bronchopulmonary proliferation. A further developmental causative factor noted [12, 13] is the association of bronchial cysts in bronchopulmonary

TABLE I

1. Congenital Pulmonary Cysts
   a. Bronchogenic cell type
      1. Solitary
      2. Multiple
   b. Alveolar cell type
      1. Solitary (balloon cyst, pneumatocele)
      2. Multiple
   c. Bronchogenic and alveolar types combined
2. Acquired Pulmonary Cysts
   a. Bullous emphysema
   b. Subpleural blebs

sequestration found with anomalous arteries arising from the aorta to supply segments of lung.

It is easy to conceive of prenatal or postnatal "developmental defects" as the same pathologic entity, and in later life, when affected by external influences, mechanical or infectious, being thought of as acquired disease. The extraneous influences can enter the picture even before birth, or at birth and onwards, or never at all. There seems little doubt that once a cyst has a bronchial communication its behavior will be affected by mechanical and accidental influences, such as cyst wall strength, location in the lung, movement of the surrounding lung tissue, size of bronchial communication, valve mechanisms in the communication, and the presence or absence of complicating respiratory infections. Most writers agree that infection in a cyst may take place by direct extension from adjacent lung or by the hematogenous route; a bronchial communication is not necessary. If there has never been a bronchial communication there can be no air in the cyst. The communication may occur at any time in life and lead by means of an expiratory check valve to the expanding single or multiple cysts. The com-



A B

FIG. 1A. (*Case 1*). X-ray of chest showing dense shadow in the right lower lobe. B. Photomicrograph of cyst wall demonstrating the pseudostratified ciliated columnar epithelium lining of the cyst, also cartilage and muscle. The wall shows inflammatory reaction.

munication with a bronchus may be temporary or periodic, as noted in a case of Peirce's,[8] where the cyst periodically evacuated its liquid contents.

After a time bronchial communication makes structural relationship difficult to demonstrate. When infection has occurred, as in some of our cases, and many of those in every series in the literature (but not in so high a proportion as found by Adams,[11] in whose series 27 out of 30 cases were found because of infection), then the pathology becomes mixed and at times confusing, as degeneration of the naturally occurring elements may have taken place. Very careful histologic search is needed to demonstrate the epithelial lining and wall structure.

Diagnosis is based on clinical, radiologic and bronchoscopic evidence. All facilities should be used, and they need not be discussed in detail. The differential diagnosis involves practically all bronchial and pulmonary disease, a list of which seems superfluous. It must be stressed, however, that the diagnosis is not easy, and that it is especially speculative if the "cyst" is bronchial in type, is solid, and has never had a bronchial communication (cases 1, 2, 3 and 4). The symptomatology and physical findings vary in each case, depending on whether the cyst is communicating with a bronchus; has or has not a check or ball valve mechanism in the bronchus and is distending; is or is not infected; and is peripherally or centrally placed, especially in reference to pressure on an adjacent large bronchus. Bacteriology and cytology are noncontributory except to assist in ruling out tuberculosis and malignancy or adenoma.

All agree that the only satisfactory treatment of bronchogenic and alveolar developmental cystic disease is surgical removal of the segment, lobe, lobes or lung involved whenever the local and general conditions permit.

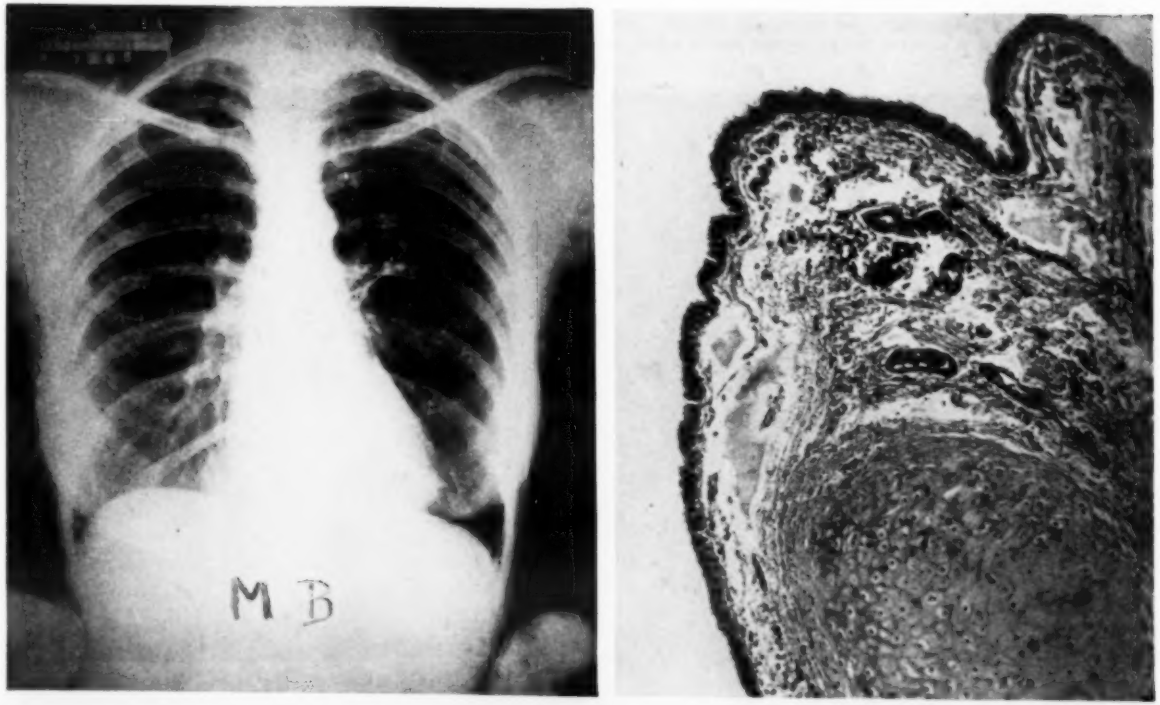
The following cases were seen by one or both of the authors in the medical and surgical departments of the Royal Victoria Hospital in the past few years.

Case Reports

Case 1. This 16 year old white male had enjoyed good general health and normal development and school progress. There was night wheezing on and off from four years of age, also occasional wheezing and right sided chest pain after strenuous exertion. No x-rays were taken prior to a routine school film in 1949. This film revealed a tricornuate shadow in the right lower lobe (figure 1A). This lay outside the bronchial tree of the lobe, which could be identified on bronchogram and was pushed aside around the shadow. Bronchoscopy was unremarkable.

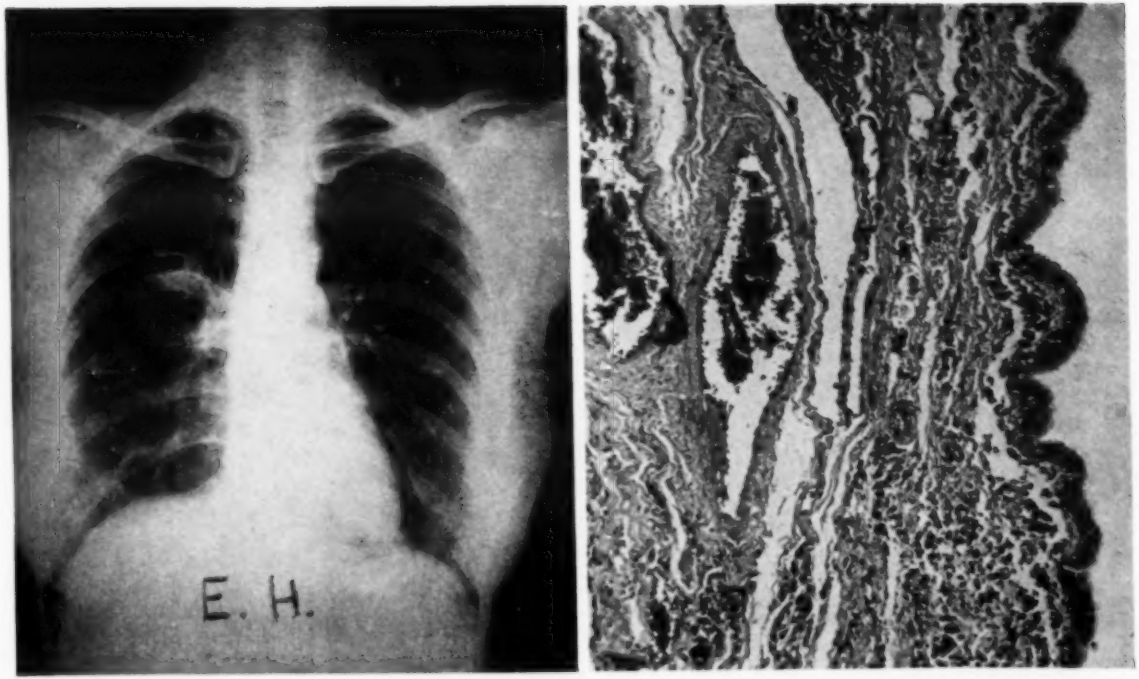
Right lower lobe lobectomy was done in June, 1950. At operation the mass could be felt in the lower lobe, which had an extra but partial fissure giving, to all intents and purposes, four lobes on the right side.

Pathologic Report (figure 1B): On section, a large multilocular, smooth walled cyst was found which measured 4 by 2 by 2 cm. and contained thick brown purulent material. The vessels in the region of the cyst were markedly dilated. Sections of the cyst showed the internal lining to be very poorly preserved but revealed pseudostratified ciliated columnar epithelium, mucous glands in patches, and cartilage and muscle in several areas. The wall showed inflammatory reaction.



A B

FIG. 2A. *Case 2.* X-ray of chest showing a small but dense shadow at the upper border of the left hilus. B. Photomicrograph of cyst wall demonstrating the ciliated columnar epithelium, glands and cartilage.



A B

FIG. 3A. *Case 3.* X-ray of chest showing the fairly dense rounded mass in the locality of the pectoral division of the right upper lobe. B. Photomicrograph of cyst wall demonstrating ciliated columnar epithelium and some inflammatory changes.

The postoperative course was uneventful and the patient's present health is good.

Case 2. This 49 year old healthy female was admitted for investigation of a small shadow found on routine chest x-ray. The only illness prior to the present investigation was a left upper lobe, low grade, long lasting pneumonitis in 1935. X-ray reports of that time suggested an enlarged left hilar shadow in the upper border and irregular accentuation of the left upper lobe tree. No investigation was made at that time. Routine x-ray (figure 2A) in 1951 revealed a small shadow in the left upper lobe just above the hilus. This mass obstructed the left upper lobe bronchus on bronchogram. Bronchoscopy was noncontributory.

FIG. 4. *Case 4.* Photomicrograph of cyst wall demonstrating ciliated pseudostratified cylindrical epithelium and a fragment of cartilage. Inflammatory reaction can be noted.

Left upper lobe lobectomy was performed successfully in April, 1951. On pathologic examination (figure 2B), the specimen showed a small cyst, 1.5 cm. in internal diameter and filled with creamy white fluid and with a septum running across it. The remainder of the lobe was atelectatic. Microscopically the cyst had a lining of ciliated columnar epithelium. The wall was thin, with some collagenous fibrous tissue but no muscle. There were foci of cartilage and glands. No bronchial connection could be demonstrated. There were several other similar and smaller cyst areas. There were no inflammatory changes.

Postoperatively there was a temporary psychotic state, which cleared well. The patient's present health is good.

Case 3. This 50 year old female's past history was unremarkable until a right sided pleurisy in 1940 and a shadow were noted in the right midlung field. X-rays at that time were done in Hungary and are not available. There was another attack of right chest pain in 1949. The patient came to Canada in early 1950 and shortly after arrival complained of episodes of minor pain in the right chest. Routine x-rays revealed the mass in the right midlung field (figure 3A).

Physical findings on admission were unremarkable. O.T. 1/1000 was positive; bacteriology was noncontributory.

Exploratory thoracotomy was done in February, 1951. The mass was found to be in the pectoral division of the right upper lobe, with inflammatory reaction extend-

FIG. 5. *Case 5.* Photomicrograph of cyst wall demonstrating a cup crypt in the cyst with better preserved ciliated pseudostratified epithelium.

ing across the fissure into the right middle lobe. The pectoral segment and right middle lobe were removed uneventfully.

Pathologic examination (figure 3B) showed a firm localized mass which contained a cavity 3 cm. in diameter, filled with creamy material. The cavity was lined by ciliated columnar epithelium. The wall was quite thick and fibrotic, with some inflammatory changes and areas of ulceration. These were covered with macrophages containing blood pigment. No muscle or cartilage was present. There was some interstitial fibrosis but no tubercle formation or caseous necrosis.

Progress has been satisfactory.

Case 4. This 51 year old woman enjoyed good health until a pneumonia in 1950. From that time she had chronic dry cough and fatigue. There was an episode of "flu" for six weeks in February, 1951, with severe cough, increased by lying down, but very little yellow sputum. Tightness in the chest and chronic fatigue continued. Weight loss was 12 pounds in two years. She was admitted in September, 1951. Alteration in breath sounds was found over the left hilus posteriorly. Chest postero-anterior and lateral films showed an area of increased density opposite and behind the left hilus, with diminished aeration of the left lower lobe. (This x-ray did not reproduce well for slide or figure.) Bronchogram showed slight narrowing of the left main stem bronchus and a pressing downward by the previously noted shadow.

FIG. 6. *Case 6.* Photomicrograph of cyst wall demonstrating the ciliated pseudostratified cylindrical epithelium.

The superior segmental branch of the left lower lobe showed irregularity of filling. Bronchoscopy showed low grade inflammation in the left lower lobe branches. Bacteriology was noncontributory. Cytology on sputum and bronchoscopic aspiration showed no malignant cells.

Left lower lobe lobectomy was performed in September, 1951.

Pathologic Report (figure 4): Adjacent to the main bronchus of left lower lobe there was a mass 4 cm. in diameter. On the cut surface it was seen to have a multiloculated cystic center filled with thick green pus. The wall was firm, thick and white, and extended into the surrounding lung parenchyma in irregular fashion. No bronchial connection was found.

Microscopic: Multiple sections through the wall of the cystic cavity showed that it was lined in many areas with respiratory ciliated pseudostratified cylindrical epithelium, and that a fragment of hyaline cartilage was present in one area. Beneath the epithelium and in some denuded areas fibrous granulation was seen, heavily infiltrated with inflammatory cells. In some areas this fibrous wall was very thick and showed abscess formation.

Summary: Congenital bronchial cyst with secondary purulent infection superimposed.

Postoperative course and progress were uncomplicated, and the patient is well.

Case 5. This 19 year old female was found to have a cyst on routine x-ray in March, 1950. (This x-ray did not reproduce well for slide or figure.) There were no previous illnesses and no symptoms or complaints. Investigation was noncontributory. The cyst pushed the bronchi of the left tree downward, forward and medially. All the left upper lobe bronchi were present. Left upper lobe lobectomy was performed in June, 1951.

Pathologic Report (figure 5): A large cyst cavity was present, the wall of which was composed of fibrous tissue and lined with compressed and flattened columnar epithelium. The cyst was multilocular, and in the crypts the epithelium was better preserved, pseudostratified and ciliated.

Postoperative course and subsequent progress were good.

Case 6. This four year old boy appeared well until 1935, when at one year of age he had an acute pulmonary infection followed by chronic cough and copious purulent sputum. Investigation in late 1937 and early 1938 revealed widespread bronchiectasis throughout the left lung with many cystic areas. No x-rays are available. Bacteriology showed mixed flora. In March, 1938, a left lower lobe lobectomy was done.

Pathologic Report: The tissue showed numerous irregular spaces lined with pseudostratified cylindrical epithelium. A cavity 3 by 1.5 cm. with similar lining was found near the hilus of the lobe (figure 6).

In September, 1938, the left upper lobe was removed. The pathologic opinion was multiple bronchiectatic cystic areas of developmental origin, showing larger and smaller thick walled, ductlike structures, the largest measuring 1.5 cm. in diameter, lined with ciliated pseudostratified cylindrical epithelium forming many papillary projections into the lumen. Occasional small abscesses were found. The parenchyma was atelectatic.

The patient made a satisfactory post-operative recovery.

The present status is not known.

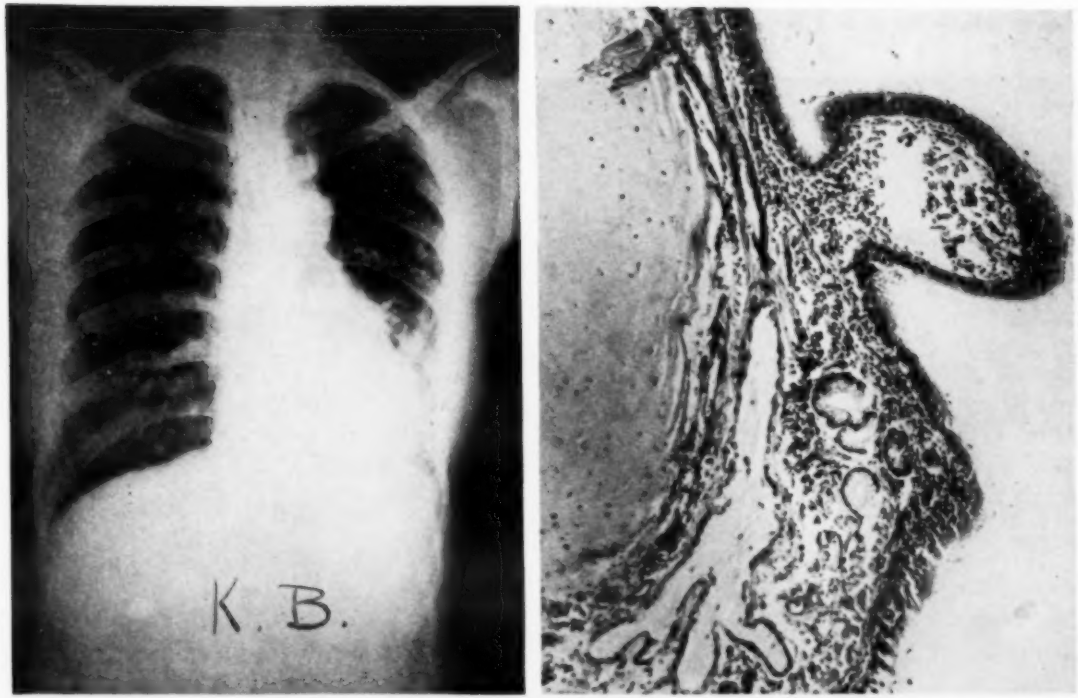
Case 7. This 32 year old female had had spasmodic cough from infancy, with much creamy, frothy and at times blood streaked sputum. Two frank hemoptyses had occurred. She was subject to frequent respiratory infections. Following the raising of the periodic bursts of copious sputum she would feel subjectively better. In the two years before admission, cough, sputum and fatigue had increased, and the patient had a dragging pain in the left chest.

On examination the only findings of interest were the diminished breath sounds and voice sounds over the lower half of the left chest, with tubular sounds over the hilus.

Investigation: Electrocardiogram was unremarkable. Bacteriology was noncontributory. X-ray opinion on films and bronchogram: cystic bullae left upper lobe, bronchiectasis left lower lobe; right side normal (figure 7A).

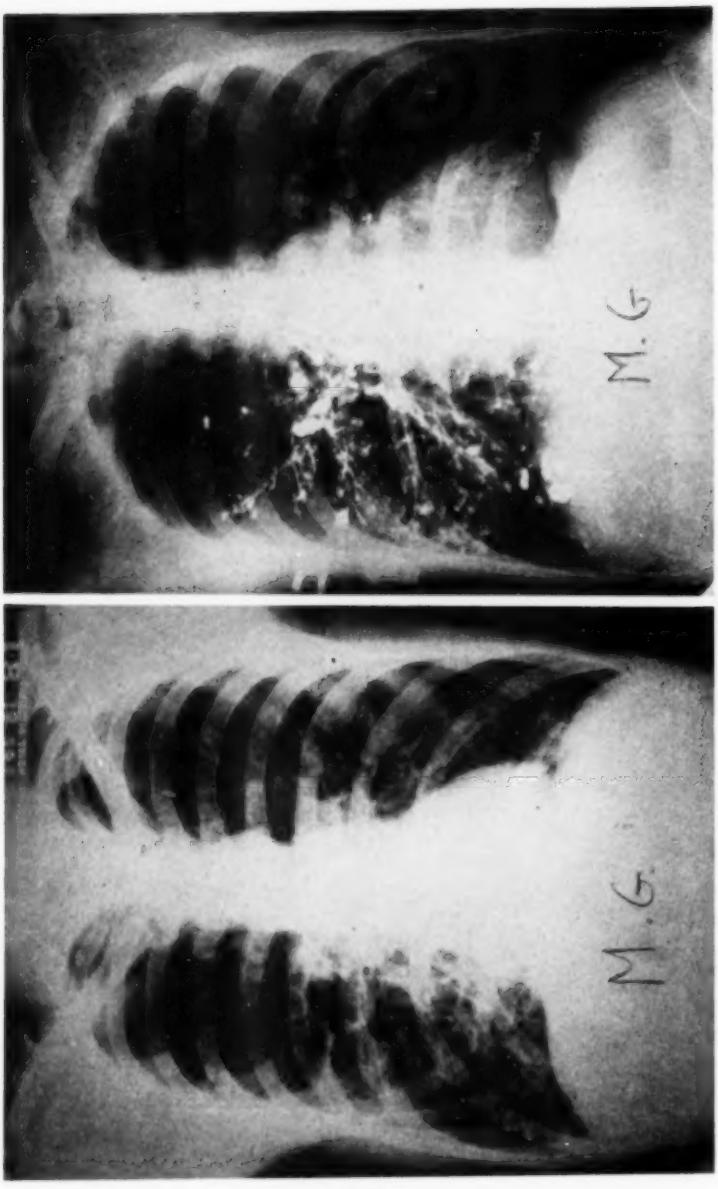
In September, 1948, a left pneumonectomy was performed.

Pathologic Report (figure 7B): The whole lung presented the appearance of a large, markedly distorted honeycomb, with thin walled cystic cavities varying from



A B

FIG. 7A. *Case 7.* X-ray of chest showing the multiloculated cystic left upper lobe and dense lower lobe. Note the shift of the mediastinal structures to the left. B. Photomicrograph of cyst wall demonstrating the ciliated pseudostratified columnar epithelium, glands and cartilage.



A B

FIG. 8A and B. *Case 8.* X-ray and bronchogram (right side only, the left side was similar) showing the multiple cystic and bronchiectatic areas, most noticeable on the right side.

pinhead to 4.5 cm. in the upper lobe and small, yellow rimmed, thick walled cystic cavities in the lower lobe. The microscopic picture of the cystic areas was the prominent feature: "These are lined by typical respiratory ciliated pseudostratified columnar epithelium, in some areas flattened and attenuated. The epithelium is supported by loose and dense connective tissue, lightly to moderately infiltrated with lymphocytes, plasma cells and macrophages and in turn supported by a smooth muscle layer, glands and irregular cartilage plaquets—present in some areas, partially or totally absent in others."

Postoperative course and progress have been good.

Case 8. This 30 year old male had had known chest disease from the age of three years, when he was in hospital for a year. He was first seen by one of us in March, 1950, because of chronic cough for as long as he could remember, variable amounts of yellow-green thick sputum over the years, shortness of breath increasing since 1948, fatigue, weight loss and weakness. He was admitted for investigation of probably cystic disease of the lungs. He admitted to having had clubbed fingers and toes all his life. This was very marked. Other pertinent physical findings were large infected tonsils, enlarged tender cervical glands, prominent left hemithorax, diminished excursion of the right base, coarse moist bubbling râles over the right middle and lower lobe area, and a variable, palpable and audible friction rub in the right axilla.

Investigation: Standard chest x-rays and bronchography demonstrated cystic disease of the left lower lobe, the right lower and middle lobes, and the right upper lobe. There was an anomalous distribution of the bronchi of the right upper lobe, with the superior segment of the lower lobe arising from the upper lobe bronchus. Some of the cystic areas did not have apparent bronchial communications but contained air and suggested gross bullous spaces (figure 8A and B).

Surgery was out of the question, due to the unforeseen extent of the cystic disease. The original feeling was that the disease involved only the right middle and lower lobes. He is being carried on a medical régime but is unable to work because of fatigue and shortness of breath.

In the above series of cases, four were solid cysts which at no time demonstrated a bronchial communication, though in cases 1, 3 and 4 there was evidence of low grade chronic infection which presumably spread from adjacent diseased lungs. One case had an air-containing but uninfected cyst. The other three cases are good examples of multiple developmental bronchial cysts with free bronchial communications, frequently referred to in the literature as congenital cystic bronchiectasis or "honeycomb lung." Two of these cases were treated successfully surgically. The third presented such widespread bilateral disease that surgery was impossible; the patient continues fairly well, though unable to work, and is on a medical régime.

Summary

The problem of congenital or, as we prefer, developmental bronchial and alveolar cystic disease has been discussed. Reference is made to a simple classification. The pathogenesis is commented upon. Eight cases of bronchial cyst are presented.

BIBLIOGRAPHY

1. Koontz, A. R.: Congenital cysts of the lung, Bull. Johns Hopkins Hosp. **37**: 340, 1925.
2. Schenck, S. G.: Congenital cystic disease of the lungs, Am. J. Roentgenol. **35**: 604, 1936.
3. Cooke, F. N., and Blades, B.: Cystic disease of the lungs, J. Thoracic Surg. **23**: 546, 1952.
4. Mayer, E., and Rappaport, I.: Developmental origin of cystic, bronchiectatic and emphysematous changes in the lungs, Dis. of Chest **21**: 146, 1952.
5. Peirce, C. B., and Dirkse, P. R.: Pulmonary pneumatocele, Radiology **28**: 651, 1937.
6. Peirce, C. B.: Cystic disease of the lung, Am. J. Roentgenol. **44**: 848, 1940.
7. Dickson, J. A., Clagett, O. T., and McDonald, J. R.: Cystic disease of the lungs and its relationships to bronchiectatic cavities, J. Thoracic Surg. **15**: 196, 1946.
8. Moersch, H. J., and Clagett, O. T.: Pulmonary cysts, J. Thoracic Surg. **16**: 179, 1947.
9. Brantigan, O. C.: Cystic disease of the lung, Dis. of Chest **15**: 192, 1949.
10. Strode, J. E.: Cystic disease of the lung, J. Thoracic Surg. **18**: 404, 1949.
11. Adams, W. E.: Differential diagnosis and treatment of congenital cystic malformations of the lung, Dis. of Chest **15**: 60, 1949.
12. Bruwer, A., Clagett, O. T., and McDonald, J. R.: Anomalous arteries to the lung associated with congenital pulmonary abnormality, J. Thoracic Surg. **19**: 957, 1950.
13. Kergin, F. G.: Congenital cystic disease of lung associated with anomalous arteries, J. Thoracic Surg. **23**: 55, 1952.

PURE MITRAL INSUFFICIENCY OF RHEUMATIC ORIGIN IN ADULTS*

By E. R. Movitt, M.D., F.A.C.P., and B. Gerstl, M.D.,
Oakland, California

Appraisal of the significance of systolic murmurs has undergone various changes in the last few decades. Originally it was thought that every patient with a systolic murmur had heart disease. Thus a diagnosis of mitral insufficiency of rheumatic origin was frequently made solely on the basis of an apical systolic murmur. Many a prospective recruit with such a murmur was rejected for military service even in the absence of any other evidence of cardiac involvement. This point of view was prevalent here and abroad before the first World War. However, as many a soldier with a systolic apical murmur not only underwent the duress of a long and exacting campaign without any evidence of a physical handicap but also continued to do well through the succeeding years of civilian life, serious doubt was cast on the significance of the murmur in question. Largely owing to the influence of Sir James Mackenzie, the pendulum swung to the diametrically opposite position, with the result that systolic murmurs came to be regarded as having no clinical significance. Of course, neither of the extreme views did justice to the case. In fact, Mackenzie himself did not intend the systolic murmur to fall into such disrepute. The present generation of physicians is witnessing the development of new teaching on this subject, with revival of interest in systolic murmurs and a more accurate appraisal of their true significance. The murmur is being evaluated in the context of the total situation in which it is found, instead of being treated in isolation. Thus, for example, a systolic apical murmur first heard in the course of an active rheumatic process is thought to be due merely to dilatation of the left ventricle incidental to rheumatic myocarditis; if seen to persist after the subsidence of the acute inflammatory stage, it is regarded as probably representing a beginning organic and permanent valvular damage. If the murmur is loud it is again thought to be a sign of organic involvement, or at least to reflect a change in circulatory dynamics. However, so vehement was the reaction to the original stand that the notion is still prevalent among many physicians that such murmurs can be disregarded. Perhaps the survival of this view explains the reluctance to make a diagnosis of isolated mitral insufficiency of rheumatic origin.

Sample quotations from modern standard texts and reference works on cardiology illustrate the still prevailing view regarding the existence of pure mitral insufficiency: "Accurate diagnosis of disease of the mitral valve depends upon the recognition, not of mitral regurgitation but of mitral ob-

* Received for publication December 22, 1952.
From the Departments of Medicine and Pathology, Veterans Administration Hospital, Oakland, California.

struction."[1] "Mitral regurgitation and mitral stenosis are almost invariably combined pathologically."[2] "Pure mitral regurgitation of rheumatic origin, without any evidence of stenosis is rare. Often the stenosis is silent and no diastolic murmur is audible."[3] "Although stenosis of the mitral valve frequently exists without associated regurgitation, regurgitation rarely occurs without stenosis."[4] Still another reason for such statements is the fact that most patients who, on physical examination, display no evidence of any lesion other than mitral regurgitation sooner or later develop the signs interpreted as indicating mitral stenosis, or are later found at autopsy to have mitral stenosis or even aortic stenosis instead. In other words, the conclusion is drawn to a large extent from the postmortem material. Levine[5] aptly criticizes the latter basis for the conclusion that organic mitral insufficiency does not exist by stating: "The difficulty with this point of view is that we cannot deny the presence of a disease which is generally nonfatal by the use of autopsy data. It would be just as fallacious to maintain that acute tonsillitis and chickenpox are extremely rare because one almost never finds cases at autopsy."

In pediatric practice one may well expect to see pure organic mitral insufficiency at necropsy more frequently than in adults, as children are more apt to die during an active rheumatic process. In fact, in 100 postmortem examinations on individuals who succumbed to rheumatic heart disease in the first two decades of life, Bland, White and Jones[6] observed 25 in which the mitral valve was deformed but there was no anatomic stenosis. "Recrudescence of rheumatic infection was the outstanding cause of death in this series and was directly responsible for the fatal issue in 85 instances." Five other deaths were due to postoperative complications, seven died from subacute bacterial endocarditis, and one each from tuberculous meningitis, typhoid fever and pulmonary abscesses. Stenosis takes time to supervene. According to the above quoted authors, "The evolution of the early alterations of the mitral cusps as a result of rheumatic fever follows a consistent course," and "The development of important scarring and deformity of the mitral valve requires a considerable length of time." They further point out that it takes at least two years for important valvular deformity of the mitral valve to occur. In contrast to the experience in pediatric practice, pure mitral insufficiency at necropsy in the adult population would be expected to occur less frequently. However, we have observed five such cases in a series of 44 autopsied patients with rheumatic heart disease. Four of them died in congestive heart failure. Yet Levine[5] states: "Fatalities from heart failure occur but rarely during the stage of mitral insufficiency so that ordinarily we have no opportunity to confirm the diagnosis at the autopsy table." He adds: "There is one circumstance that does occur which enables us to see the mitral valve during the stage of organic insufficiency without stenosis, i.e., subacute bacterial endocarditis. In this way a fatal disease develops in a patient who had only a systolic murmur long before

congestive heart failure would otherwise have occurred and we are permitted to examine a mitral valve that is diseased but not stenotic." Yet bacterial endocarditis was present in only one of four patients, and this patient died in congestive heart failure at the age of 42. The other three died in congestive heart failure at the ages of 50, 51 and 56, respectively. The latter occurrence is rare, according to Levine and others. Thus Friedberg [7] states: "Heart failure resulting from pure mitral insufficiency is uncommon, except in the cases due to spontaneous or traumatic rupture of chordae or cusps." However, as early as 1926 Sprague and White [8] were suspecting that the rôle of mitral insufficiency in the production of heart failure had been excessively depreciated. They postulated pure organic mitral regurgitation of rheumatic origin as a clinical entity, but added: "It is not demonstrated at necropsy as it is rarely if ever fatal." Levine [5] concedes: "On rare occasions organic mitral insufficiency without stenosis does lead to progressive cardiac enlargement even with marked dilatation of the left auricle and congestive failure."

Dana [9] reported from the Boston City Hospital that in his series of 150 cases showing endocarditis of the mitral valve at necropsy, he found six "who would seem to have died of no cause other than secondary to pure mitral regurgitation," uncomplicated by lesions of other valves or by pericarditis. Unfortunately, the ages of the patients are not stated, with one exception (a 50 year old man). As already mentioned, the death of a child who is found at necropsy to have only mitral insufficiency without stenosis is not a rarity. Neither is it indicated in Dana's series whether the patients died in congestive heart failure. Also, Dana's criterion for postulating the existence of insufficiency without stenosis is perhaps open to criticism. He divided his cases into two groups: those with mitral valve measuring 8 cm. or more, and those measuring less than 8 cm. The cases showing a circumference of 8 cm. or more at the mitral valve were classified as mitral endocarditis without stenosis, or as mitral regurgitation. The state of the valve cusps, particularly with regard to the presence or absence of any fusion, is not described.

In the group of 44 cases of rheumatic heart disease autopsied at this hospital, we found five instances of pure and isolated mitral valve incompetence without deformity of any other valve, pericarditis, hypertension, coronary artery disease, syphilis or any other type of cardiac involvement but rheumatic, with the sole exception of bacterial endocarditis in one case. In none of these five patients was an active rheumatic process suspected during life, nor was there any evidence of it on microscopic examination. As one of these patients, aged 58, did not die of heart disease, he is not included in the group of four patients reported here, all of whom died in congestive heart failure. Yet it is appropriate to note in passing that the case excluded from the present series presents still another instance of pure mitral insufficiency in a 58 year old person.

Case Reports

Case 1. A 56 year old white male plaster finisher was admitted to the hospital with complaints of shortness of breath, palpitations and edema of the legs. He had been in good health until 1918, when he developed shortness of breath, a fluttering of the heart and easy fatigability. He has been conscious of his difficulties ever since, and has limited his work to accommodate this disability. In 1931 he was hospitalized elsewhere for treatment of pneumonia, at which time he was told that he had a "weak heart." He was placed on digitalis and has continued to take digitalis intermittently ever since. Dyspnea progressed in severity, and there were frequent attacks of pal-

FIG. 1. (*Case 1*) Photograph of the heart. Mitral ring measures 14.2 cm. in length.

pitations. In November, 1951, the patient noticed swelling of the ankles for the first time. A regimen consisting of a salt-free diet, digitalis and mercurial diuretics was instituted, with some improvement. However, two weeks prior to admission, dyspnea became more marked and the ankle edema reappeared. In 1923 the patient had an acute attack of "infectious" arthritis involving both knees, with redness, swelling and limitation of motion. The attacks lasted about two weeks. He had had frequent nosebleeds in early life.

The patient was a well developed and well nourished orthopneic man. Cervical

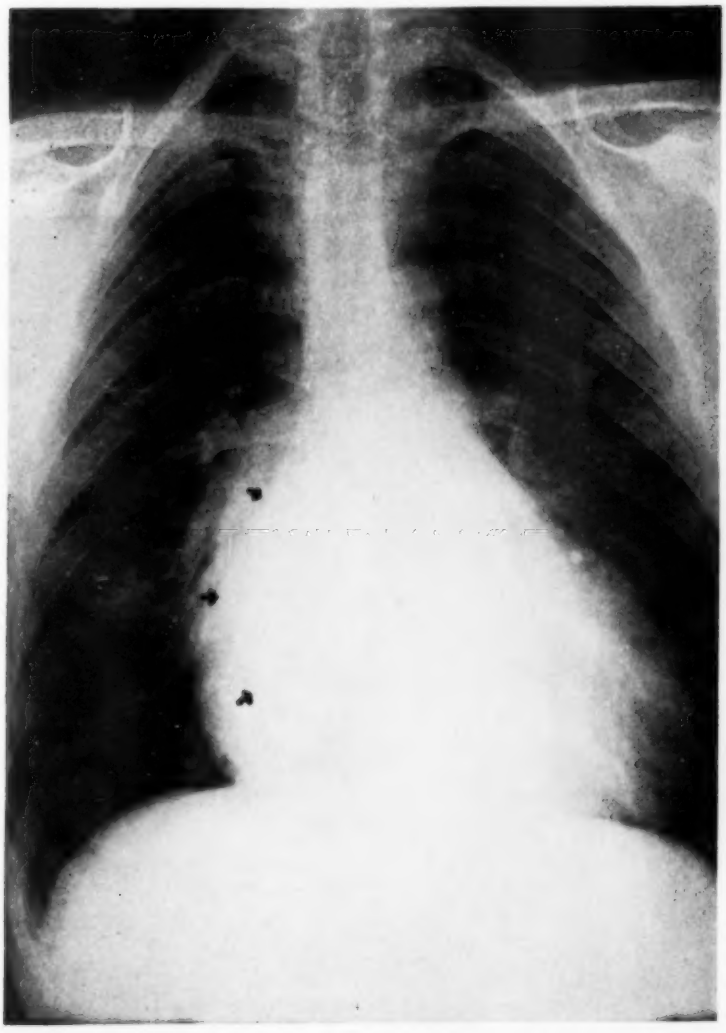


FIG. 2*A*. (*Case 3*) Roentgenogram of the heart. Postero-anterior view. Arrows point to the right border of left auricle.

veins were engorged. A pronounced systolic thrill was felt at the apex of the heart. The left border of cardiac dullness to percussion extended to the midaxillary line. The point of maximal impulse was diffuse over the fifth and sixth intercostal spaces in the axilla. The second pulmonic sound was accentuated. The second aortic sound was present. There was a loud, harsh systolic murmur heard over the entire precordium, of maximal intensity at the apex, with transmission into the carotid

arteries, axilla, both lung bases and along the spine as far down as the sacrum. The rhythm was totally irregular, with a rate of 120 and a pulse deficit of about 20. Blood pressure was 125 mm. Hg systolic and 95 mm. diastolic. Crepitant râles were heard at both lung bases. The abdomen was somewhat distended, and it was thought that a fluid wave could be elicited. A slightly tender liver was palpated 5 cm. below the right costal margin. Moderate pitting edema was present over the lower extremities.

Urinalysis showed specific gravity of 1.020, with a trace of albumin and a mod-

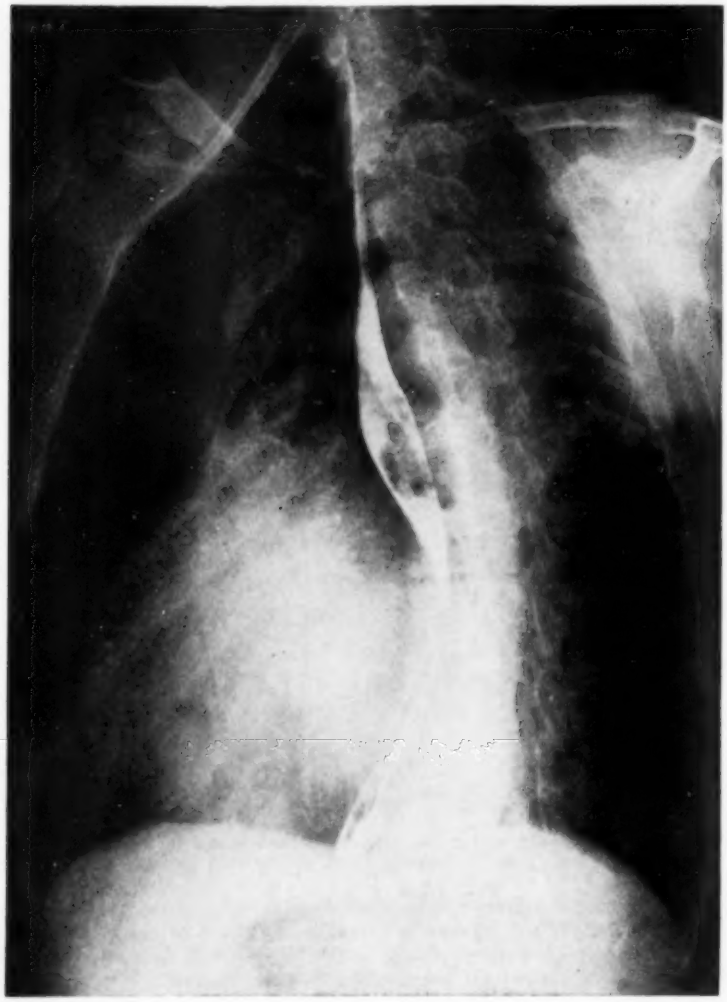


FIG. 2B. (*Case 3*) Roentgenogram of the heart. Right oblique view demonstrating left auricular enlargement.

erate number of hyaline casts. The red cell count was 4.3 million, with 9.7 gm. of hemoglobin. The white cell count was 11,000, with 72 per cent neutrophils and 18 per cent lymphocytes. Serologic tests for syphilis were negative. Sedimentation rate was 2 mm. in one hour (Westergren). Blood urea nitrogen was 53 mg. per cent. The blood culture showed no growth. Roentgenogram of the chest and fluoroscopic study demonstrated marked cardiac enlargement, consisting principally of enlargement of the left auricle and left ventricle. The left auricle projected posteriorly and to the right but did not present itself on the right cardiac border. An electrocardiogram showed auricular fibrillation, with suggestive evidence of right ventricular hypertrophy. Arm-to-tongue circulation time with Decholin was 40 seconds.

The patient ran an afebrile course. He was placed at bed-rest with a low salt diet, digitalis and mercurial diuretics. Increasing doses of digitalis finally reduced the ventricular rate to between 80 and 90. An attempt at conversion to regular sinus rhythm was made with quinidine, with doses up to 0.6 gm. every six hours. The blood pressure fell to 80 systolic and 65 diastolic. At the same time the patient was seen to be quite lethargic. Because of a drop in blood pressure and lethargy, quinidine was discontinued. Although the patient improved somewhat, the heart failure was refractory to treatment and he died on the twenty-seventh hospital day.

Necropsy: At autopsy there was marked edema over both legs. About 1,000 c.c. of dark yellow, clear fluid were present in the right and 700 c.c. in the left pleural cavity. The pericardial sac contained 100 c.c. of clear dark yellow fluid.

Heart: This was a large, flabby organ, weighing 800 gm. The epicardial surface was intact with the exception of a small plaque of fibrin over the right auricular appendage. The right atrium was markedly distended and contained a fist-sized postmortem clot. The auricular appendage was almost entirely filled by firmly adherent thrombi. Upon sectioning, the right ventricular space was enlarged, although there was no bulging of the papillary muscles. The tricuspid and pulmonic valves were delicate. The left auricle and auricular appendage were smaller than the right, their endocardium was intact, and there were no thrombi. The mitral ostium easily admitted four fingers. Almost the entire width of the mitral valve was diffusely thickened, and only a narrow zone at the root was delicate. Its surface was warty and light yellow, and the consistency was moderately firm. No vegetations were seen. Some of the chordae tendineae were thicker than usual. The endocardium over the ventricular wall and septum was delicate. There were no thrombi. The aortic valve was delicate. The coronary ostia and coronary vessels were widely patent and practically free of sclerosis. The right and left ventricles were of approximately the same size, and on the left likewise there was no bulging of the papillary muscles. The measurements of the valves were: tricuspid, 14.2 cm.; pulmonic, 7.4 mm.; mitral, 14 cm.; aortic, 7.8 cm. The right ventricular wall near the apex measured 4 mm.; the left 12 mm. without the papillary muscles.

Aorta and Major Vessels: The major veins were congested but free of thrombi. The aorta showed numerous small yellow streaks but there were no ulcers or thrombi.

Lungs: These were large organs weighing 1,220 (right) and 890 gm. (left). Their air content was diminished, and a large consolidated area was found in the lateral segment of the left lower and the basal segment of the right lower lobe. Here the pleura was dark purplish and bulging. The sectioned surface was rusty brown, and a large amount of brownish, frothy fluid escaped. The consolidated areas corresponded to infarcts measuring 10 by 8 cm. in the right and 6 by 7 cm. in the left lower lobe. A 3 mm. branch of the left pulmonary artery supplying the infarcted area and the main artery of the right lower lobe were occluded by moderately firm, adherent thrombi.

Liver: The liver weighed 2,200 gm. Its capsule was intact. On sectioning there was a distinct nutmeg appearance.

Spleen: The spleen was of medium size and weighed 180 gm. Its capsule was intact. The parenchyma was dark purple and moderately firm, and a moderate amount of splenic pulp could be scraped off.

Kidneys: These were large and weighed 270 gm. each. The capsule stripped with ease, revealing a smooth purplish surface. Cortex and medulla differentiated well, and the architecture was seen to be well preserved.

Microscopic Examination: Heart: Numerous small scars not confined to the perivascular spaces were present throughout the left myocardial wall. Some of the intact muscle fibers showed evidence of hypertrophy. Aschoff's bodies were not seen. Numerous coarse collagen fibers comprised the central part of the thickened mitral valve, with somewhat cellular connective tissue laid upon it. Only in a few places was the connective tissue more cellular. Vascularization was poor. There was no evidence of vegetations or microörganisms (Gram stain). At the root of the mitral valve a few lymphocytes were noted scattered between the adjacent muscular fibers. The thrombus of the right auricle showed advanced organization, with a few scattered chronic inflammatory cells beneath the endocardium.

Lungs: The sections of the infarcted areas showed a hemorrhagic exudate and, in places, complete necrosis of the parenchyma. Several branches of the pulmonary artery were occluded by thrombi with peripheral organization. There was slight to moderate intimal proliferation in these arteries. Elsewhere, the majority of

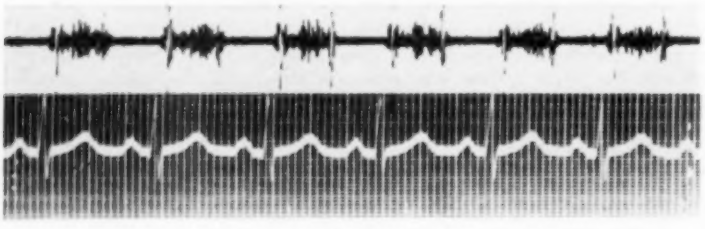


FIG. 3. (*Case 2*) Phonocardiogram.

alveoli were filled by large numbers of macrophages laden with brown granular pigment (heart failure cells). In a few places there was slight thickening of the alveolar septa, as well as plugging of the alveolar spaces by cellular connective tissue. Several of the medium sized pulmonary arteries showed a thickened, hypertrophied wall and narrowed lumina.

Liver: There was marked congestion of the central veins and of the capillaries, frequently causing compression or complete disappearance of liver cells. No cellular infiltrations were noted. The portal spaces were free of changes.

Spleen: The sinusoids of the red pulp were congested.

Kidneys: A few small subcapsular scars with hyalinization of glomeruli were noted. Elsewhere the glomeruli were well preserved, although there were some with slight thickening of Bowman's membrane. A small amount of granular pink staining material was seen in the glomerular space as well as in the collecting tubules and on the loop of Henle.

Case 2. A 42 year old Filipino male was admitted to the hospital with complaints of palpitation, loss of weight despite good appetite, nervousness and insomnia, all of about two months' duration. During this period he had also experienced a few chills. There was a history of some exertional dyspnea of several years' duration. When at one time in the past the patient was hospitalized for back strain, he was told that

there was something wrong with his heart and that he should "take it easy." There was no history of rheumatic fever or its equivalent.

The patient was a well developed but underweight male, weighing only 101 pounds (average weight, 132 pounds). The thyroid was slightly and symmetrically enlarged. A pronounced systolic thrill was felt at the apex of the heart. The heart seemed generally enlarged on percussion. There was a loud, harsh systolic murmur heard over the entire precordium, with maximal intensity at the apex and with radiation to both lung bases and the spine as far down as the sacrum. The rhythm was regular, with a rapid rate of 100. Blood pressure was 130 systolic and 80 diastolic. The liver edge was felt two fingerbreadths below the costal margin, and the splenic edge was palpated just under the costal margin. There was a gross tremor of the fingers of both hands, and clubbing of the fingers was noted. Urinalysis showed specific gravity of 1.024, with a trace of albumin. The red cell count was 4.83 million, with 13 gm. of hemoglobin. The white cell count was 10,500, with 76 per cent neutrophils and 24 per cent lymphocytes. Serologic tests for syphilis were negative. Sedimentation rate was 11 mm. in one hour (Westergren). Serum bilirubin was 0.5 mg. per cent. Bromsulfalein test (5 mg./kg. dose) showed 8 per cent retention in 45 minutes. Cephalin cholesterol flocculation test was ± in 24 hours and 1 plus in 48 hours. Basal metabolic rate was plus 42. Roentgenogram of the chest showed enlargement of the heart with mitral configuration. Both lung roots were prominent, with considerable increase in lung markings, indicating moderate pulmonary congestion. The electrocardiogram showed regular sinus rhythm and was not in any way remarkable except for rather prominent P-waves, which were interpreted as possibly being indicative of auricular hypertrophy.

Despite the patient's practically afebrile course while in the hospital, the possibility of subacute bacterial endocarditis was entertained because of the history of chills, the cardiac murmur and splenomegaly. However, repeated blood cultures failed to show any growth. A diagnosis of thyrotoxicosis was made on the basis of the patient's history, physical findings and repeatedly and significantly elevated basal metabolic rates. On propylthiouracil, 200 mg. a day, the basal metabolic rate fell to plus 9. In the course of antithyroid treatment, thyroiditis developed, manifested by pain and tenderness over the thyroid gland, which lasted a few days. Subtotal thyroidectomy was performed. The postoperative course was essentially uneventful and the patient was discharged.

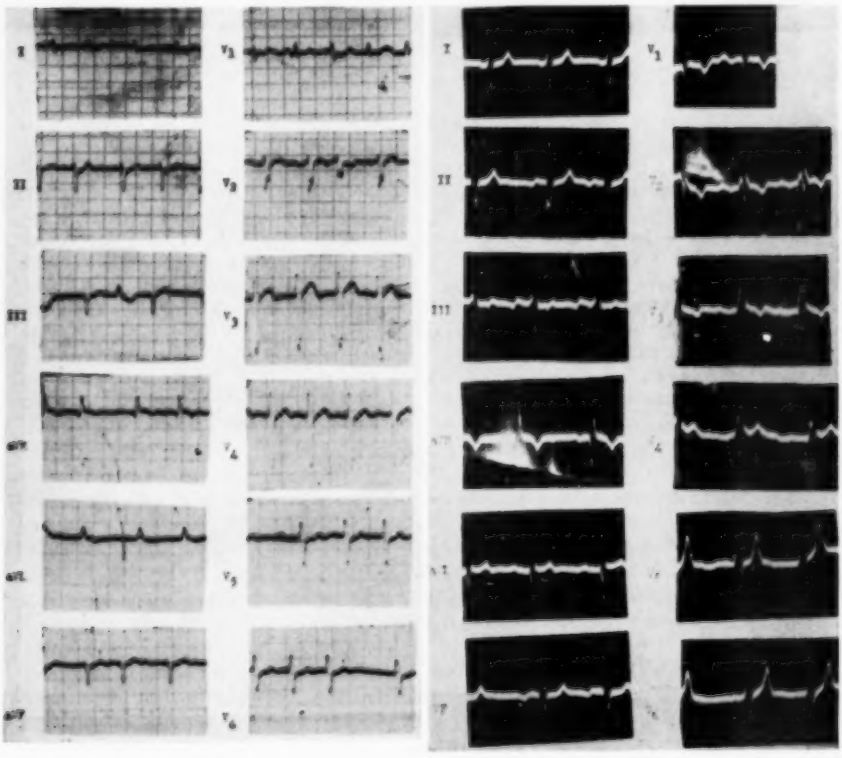
He was readmitted three months later with an interval history of increasing dyspnea, particularly marked on the day before entry, and accompanied by some precordial pain of moderate intensity.

The patient was dyspneic and cyanotic. The cardiac findings were as previously noted. Crepitant râles were heard at both lung bases. Roentgenogram of the chest showed cardiac enlargement as previously described, with pulmonary congestion. The electrocardiogram demonstrated rather striking changes when compared with the previous one: there was a right axis deviation, a tall R-wave in aVR, R-prime in V_1, V_2, V_3 and V_4, with inverted T-waves in V_1, V_2 and V_3. The tracing was interpreted as indicating right ventricular strain. The patient was placed in an oxygen tent and digitalized. However, his condition rapidly deteriorated and he died eight hours after admission.

Necropsy: At autopsy there were 500 c.c. of clear yellow fluid in the left pleural space. The pericardial sac contained 50 c.c. of clear amber fluid.

Heart: The heart weighed 450 gm. and was flabby. Several soldier's patches were noted over its anterior surface. The right auricle was enlarged and filled by postmortem clots. The papillary muscles and columnae carneae were prominent. The wall at the apex measured 2 to 3 mm., at the pulmonary cone 4 mm. in diameter.

Tricuspid and pulmonic valves were delicate and measured 12.8 and 7.2 cm. The left ventricular wall was markedly enlarged and thickened. The papillary muscles and columnae carneae were bulging. The mitral ostium was wide, with a circumference of 11.5 cm. Soft wartlike vegetations were noted over the anterior cusp. The chordae tendineae were fused or thickened and shortened. The endocardium of the auricle showed a finely uneven surface. The remaining part of the endocardium on the left was intact. The aortic valve was free of changes. The coronary vessels were not remarkable.



a b

FIG. 4. Electrocardiograms. (a) *Case 1.* The pattern is suggestive of right ventricular hypertrophy. (b) *Case 2.* The pattern is that of incomplete right bundle branch block, compatible with right ventricular hypertrophy.

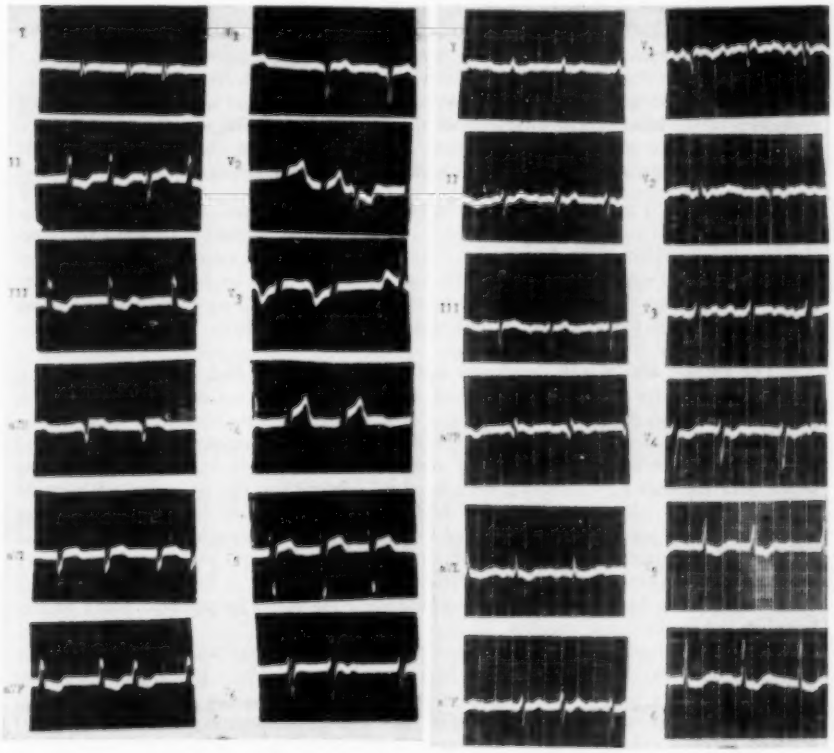
Aorta: There were a few small arteriosclerotic plaques in the thoracic and abdominal aorta. No ulcerations or thrombi were seen.

Lungs: These organs weighed 450 and 840 gm. (left and right). Both lower lobes were somewhat atelectatic. On sectioning the left lung, a large amount of brownish yellow fluid escaped from the surface of the upper lobe. Peripheral atelectasis and several foci of bronchopneumonia were noted in the lower.

Liver: The liver weighed 1,720 gm. Its capsule was tense and thickened over the lower part of the right lobe. Sectioning revealed a distinct nutmeg-like appearance in places, in others a brown, firm parenchyma.

Spleen: The spleen weighed 220 gm. Its capsule was tense. The parenchyma was purple in color. The Malpighian corpuscles were unusually large.

Kidneys: The kidneys weighed 180 gm. each. Their capsule stripped with ease, revealing a smooth purple surface. The parenchyma showed a well preserved architecture.



c d

FIG. 4. (c) *Case 3.* Prominent S-waves in all precordial leads constitute only a presumptive evidence of right ventricular hypertrophy. (d) *Case 4.* There is nothing to suggest either right or left ventricular hypertrophy. S-T segment and T-wave changes in left precordial leads may be reflecting digitalis effect.

Microscopic Examination: Heart: The fibrillary structures of the muscle fibers were well preserved in parts of the section, less well preserved in other parts. There were no cellular infiltrations or Aschoff's bodies. The blood vessels were congested. The coronary vessels were free of changes. The root of the mitral valve was thickened by hyalinized connective tissue. Toward its edge, cellular connective tissue formed polyp-like protrusions. Globular brown-yellow pigment was deposited in the

connective tissue. Pink-staining granular material, as well as cellular debris, polymorphonuclear leukocytes and fibrin, was seen at several points on the surface. At the edge of the cusp there were numerous clumps of small gram-positive staining cocci. The endocardium of the left auricle was thickened by connective tissue upon which was laid an exudate of partly disintegrated acute inflammatory cells.

Lungs: Engorgement of the alveolar capillaries was seen throughout the sections. Many alveoli contained groups of large mononuclear phagocytes laden with a brown granular pigment. Elsewhere the alveolar exudate consisted of granular pink-staining material and a varying number of red blood cells. Slight interstitial fibrosis was sometimes noted.

Liver: The central capillaries were maximally congested, and the liver cells were compressed and sometimes replaced by small hemorrhages.

Spleen: The Malpighian corpuscles were large and showed well developed germinal centers. Ribbons of homogeneous pink-staining material were deposited in the reticulum of the latter. The sinusoids of the red pulp were congested.

Kidneys: The glomerular capillaries were distended, but the glomerular architecture was well preserved. The tubules showed postmortem changes.

Case 3. A 51 year old male retired railroad employee was admitted to the hospital with complaints of abdominal fullness, vomiting and nocturnal dyspnea of about two weeks' duration. He had had a moderate amount of exertional dyspnea for several years. Twenty years before he had been told that he had rheumatic heart disease but had no symptoms referable to this at that time. Ten years before he had had palpitation of the heart for which digitalis was prescribed. There was no history of rheumatic fever or its equivalent.

The patient was a well developed and fairly well nourished man, not appearing to be in any acute distress. There was no dyspnea, cyanosis or edema. The left border of cardiac dullness extended to 2 cm. beyond the midclavicular line in the fifth intercostal space. The second pulmonic sound was accentuated. The first mitral sound was rather loud and somewhat snappy. A loud harsh systolic murmur was heard over the entire precordium, with maximal intensity at the apex and with transmission well out into the axilla. (In this case and the one to follow, the palpatory and auscultatory cardiac findings were unfortunately less completely recorded than in the first two patients.) The rhythm was grossly irregular, with a rate of 85 per minute. Blood pressure was 120 systolic and 80 diastolic. A few moist râles were heard at the lung bases. A slightly tender liver edge could be palpated three fingerbreadths below the costal margin.

Urinalysis showed specific gravity of 1.027 and 1 plus reaction for albumin. The red cell count was 4.63 million, with 14.3 gm. of hemoglobin. The white cell count was 7,000, with a normal differential count. Serologic tests for syphilis were negative. Blood urea nitrogen was 19 mg. per cent. Roentgenograms of the chest showed marked enlargement of the cardiac silhouette, with definite enlargement of the left auricle. The main stem bronchus was moderately elevated by the auricular enlargement, and slight compression of the esophagus was demonstrated on fluoroscopy with barium swallow. The electrocardiogram showed auricular fibrillation, with right axis deviation and rather conspicuous S-waves in all precordial leads.

On a cardiac regimen consisting of low sodium diet, digitalis and mercurial diuretics the patient improved. He was discharged on the thirty-second hospital day.

The patient was readmitted to the hospital 24 days after discharge. He stated that in spite of adhering to a low salt diet and taking digitalis he had developed an unproductive cough and swelling of the ankles. The patient was orthopneic. Cervical veins were distended in a semirecumbent position. Examinations of the heart revealed findings similar to those of previous admission. Blood pressure was 130 mm. Hg systolic and 80 mm. diastolic. Moist râles were heard at both lung bases.

The liver was again palpable three fingerbreadths below the costal margin. Shifting dullness was present in both flanks. There was moderate pitting edema over both lower extremities extending up to the knees, and some pitting edema over the sacral area. Cardiac regimen was resumed and improvement followed. However, on the ninth hospital day rectal bleeding started, and the patient began to vomit. Investigation of the possible causes of rectal bleeding proved fruitless. On the fourteenth hospital day some periorbital edema was noted, with increase in edema elsewhere. On the seventeenth hospital day oliguria developed. Blood urea nitrogen rose from the initial of 18 mg. per cent to 125 mg. per cent. At the end of the third week of hospitalization jaundice supervened, with a serum bilirubin of 7 mg. per cent. The patient lapsed into a semicomatose condition and died on the thirty-ninth hospital day.

Necropsy: At autopsy there was moderate edema over the dorsum of both feet.

Heart: The heart was enlarged and weighed 565 gm. Pericardium and epicardium were intact. All four chambers were dilated, particularly the left atrium. The myocardium was brown red and firm. The left ventricular wall measured 10 mm., the right 4 mm. in thickness. The circumferences of the valves were: aortic, 7.5 cm.; mitral, 14.5 cm.; pulmonic, 8 cm.; tricuspid, 15 cm. The endocardium and valve leaflets were smooth and delicate, except for the mitral valve, which was thickened, leathery and slightly beaded along the free edges. The coronary arteries were slightly tortuous, thin-walled and patent. A large mural thrombus was adherent to the endocardium of the right auricular appendage, and a smaller one to the left apex.

Aorta: The aorta and major vessels were of normal thickness and caliber. The aortic intima was pale yellow and smooth except for the posterior aspects. There was a small atheromatous ulcer on the anterior aspect of the abdominal aorta, about 1 cm. above the bifurcation. A thrombus 5 cm. in length and projecting into the right common iliac artery was attached to it.

Lungs: The left lung weighed 650 gm., the right, 600 gm. The right apex was adherent to the parietal pleura. A wedge shaped, well demarcated infarct, 6 cm. in diameter, was noted in the right lower lobe and a similar 5 cm. infarct in the left upper lobe.

Liver: The liver weighed 1,600 gm. and, on section, revealed a nutmeg appearance of the parenchyma.

Spleen: The spleen weighed 150 gm. The capsule was smooth and prune-blue. Cut sections showed a dark purplish, firm, homogeneous parenchyma. The scrapings were scant.

Kidneys: The left weighed 180 gm., the right, 220 gm. In the left kidney several wedge-shaped, pale yellow, well demarcated infarcts were noted.

Microscopic Examination: Heart: A section of the left auricle showed evidence of hypertrophy of the muscle fibers and a fibrosed endocardium but no inflammatory cells. The mitral valve was thickened by dense acellular connective tissue devoid of inflammatory cells and supplied by numerous small blood vessels. Some of the muscle fibers of the left ventricular wall were replaced by cellular connective tissue, and there was a moderate perivascular fibrosis. No Aschoff's bodies or Aschoff's cells were found. The thrombus in the right auricular appendage was fairly well organized.

Lungs: The infarcts were partly necrotic and there was dense polymorphonuclear infiltration. The bronchial lumina and the alveoli elsewhere contained masses of red blood cells.

Liver: There was marked congestion of the central capillaries and veins, with compression and sometimes disappearance of liver cells. The portal triads were not remarkable.

Spleen: Congestion of the sinusoids of the red pulp was pronounced.

Kidneys: The glomeruli were well preserved. The loops of Henle as well as the distal convoluted tubules showed flattening of the epithelium.

Case 4. A 50 year old white male was admitted to the hospital with the chief complaints of marked orthopnea, swelling of the ankles and a cough productive of some white phlegm, all of about two weeks' duration. Patient had been employed as a mechanical engineer until about four years before, when he had had to retire because of increasing shortness of breath. One year before admission he had been digitalized elsewhere with Cedilanid, and he continued to take maintenance doses up to the time of entry. There was a history of acute rheumatic fever at the age of 14 and again at the age of 22.

The patient was a well developed and well nourished middle aged man, cyanotic and orthopneic. There was palpable a systolic thrill at the apex of the heart. The left border of cardiac dullness extended to the left anterior axillary line in the sixth intercostal space. The rate was grossly irregular. The second pulmonic sound was not accentuated. A loud, rough systolic murmur was heard over the entire precordium, with maximal intensity over the apex, and transmitted well into the axilla. The blood pressure was 140 mm. Hg systolic and 85 mm. diastolic. There were moist râles heard at both lung bases. The tender liver was palpable four fingerbreadths below the costal margin; the spleen was also palpable. Moderate pitting edema was present over both ankles.

Urinalysis showed a specific gravity of 1.010 and 1 plus reaction for albumin. The red cell count was 5.1 million, with 15.9 gm. of hemoglobin. The white cell count was 16,000, with 83 per cent neutrophils and 17 per cent lymphocytes. Serologic tests for syphilis were negative. Blood urea nitrogen was 24 mg. per cent. Total serum protein was 5.1 gm. per cent, with 2.9 gm. per cent of albumin and 2.2 gm. per cent of globulin. Serum bilirubin was 0.7 mg. per cent. Bromsulfalein test (5 mg./kg. dose) showed 13 per cent retention of the dye in 45 minutes. Cephalin cholesterol flocculation test was 0 in 24 hours and ± in 48 hours. Roentgenogram of the chest revealed cardiac enlargement with a mitral configuration, heavy lung roots, increase of lung markings and possibly a small effusion at the left base. Electrocardiogram demonstrated auricular fibrillation, left axis deviation and some depression of the S-T segments in multiple leads, interpreted as being due to digitalis effect. Arm-to-tongue circulation time with Decholin was 33 seconds, and the venous pressure was 13 cm. of water.

Digitalis therapy was continued with addition of mercurial diuretics. An attempt at conversion of auricular fibrillation to normal sinus mechanism with quinidine proved unsuccessful on two occasions. However, the patient initially improved somewhat, but then his condition deteriorated and he died on the ninety-third hospital day.

Necropsy: At autopsy there was moderate edema of both lower extremities. Approximately 700 c.c. of slightly cloudy dark yellow fluid were present in each pleural cavity. The pericardial sac contained 100 c.c. of clear yellow fluid.

Heart: The heart weighed 530 gm., it was flabby and showed several reddish dull areas over the anterior surface of the right ventricle and posterior surface of the left ventricle. Otherwise the epicardial surface was intact. Except for slight thickening of the tricuspid valve the right heart was not remarkable. The mitral valve was inspected before opening the left heart. There was no evidence of stenosis. The left auricle was considerably increased in size, and its endocardium, particularly over the septum, was thickened. The left ventricular space was increased and the ventricular wall was intact. The endocardium over both papillary muscles and the chordae tendineae were thickened and yellowish in color. The posterior mitral cusp was somewhat thickened and the anterior mitral cusp was markedly and diffusely thickened. The aortic cusps were more opaque than usual but there was no deformity. The measurements of the valves were: tricuspid valve, 14.6 cm.; pulmonic valve, 7.2 cm.; mitral valve, 12.7 cm.; aortic valve, 7.6 cm. The right ventricular wall measured 3 to 4 mm., the left 8 mm. in thickness.

Aorta: A few small, slightly raised arteriosclerotic plaques were noted in all parts.

Lungs: These organs weighed 730 and 540 gm., right and left. Both upper lobes were collapsed and atelectatic, and the pleura was wrinkled. Both lower lobes and the right upper lobe showed protruding, oval shaped, dark purplish consolidated areas. A small amount of fibrinous exudate was seen over them. Upon sectioning, the upper lobes showed no changes except atelectasis and an infarct in the basal segment of the left upper lobe. There were infarcts in the left lower lobe and one in the right middle lobe.

Liver: The liver weighed 1,750 gm. The capsule was slightly hob-nailed, particularly over the left lobe. The parenchyma had a distinct nutmeg appearance, was firm, and a large amount of hemorrhagic fluid escaped from the surface.

Spleen: This was a medium sized organ weighing 200 gm. The capsule was intact. The parenchyma was firm and dark purple, and a small amount of splenic juice could be scraped off.

Kidneys: These weighed 195 and 185 gm., right and left. Their capsule stripped with ease and revealed a smooth surface. The architecture of the parenchyma was well preserved.

Microscopic Examination: Heart: Some of the muscle cells showed evidence of hypertrophy. There were no myocardial scars. An occasional group of small round cells was noted in the perivascular spaces, but cells resembling Aschoff's cells were not found. There was small round cell infiltration of the epicardium. The endocardium was moderately thickened by acellular connective tissue. At one point there was an accumulation of collagen fibers and connective tissue, with a few round cells noticeable. Fragments of recent antemortem thrombi were seen between the trabeculae. The mitral valve was made up of various layers of loosely and densely arranged connective tissue fibers, but was devoid of inflammatory cells.

Lungs: There was complete necrosis of the parenchyma, including the vessels of the infarcted areas. Scanty fibroblastic proliferations surrounded the infarcted areas. Peripherally, the alveoli were densely filled by polymorphonuclears. Several vessels were occluded by recent thrombi, and there was polymorphonuclear infiltration of their walls. The alveoli elsewhere were collapsed, and numerous mononuclear phagocytes containing a brown granular pigment were seen in them, or an exudate, containing polymorphonuclears and fibrin. In places there were interstitial thickening and cuboidal metaplasia of the alveolar epithelium. The arteries in these areas showed intimal proliferation.

Liver: There was marked congestion of the central capillaries, sometimes associated with extravasation of blood and disappearance of liver cells. Slight sclerosis of the central veins was also noted.

Spleen: The sinusoids of the red pulp were engorged by densely packed red blood cells.

Kidneys: There was slight engorgement of the glomerular capillaries, but otherwise the glomerular architecture was well preserved.

Comment

Four patients with pure insufficiency of the mitral valve, aged 42, 50, 51 and 56, respectively, all died in congestive heart failure. In addition, one patient had bacterial endocarditis. In none was there any clinical or pathologic evidence of an active rheumatic process. No valves other than the mitral were found to be deformed at necropsy. In none of these patients was there any evidence of complicating pericarditis, syphilis, congenital

lesion or degenerative type of heart disease such as that due to hypertension or coronary arterial sclerosis. Patchy myocardial fibrosis in cases 1 and 3, found in the presence of well preserved coronary vessels, was interpreted by the pathologist as probably being secondary to a functionally conditioned anoxic state. Thus, all four patients apparently died solely as a result of pure mitral regurgitation, which again is shown of itself to cause intractable, fatal congestive heart failure, contrary to the statement by Cabot [10] that "no one ever died of mitral regurgitation." We also wish to stress the fact that pure mitral regurgitation may occur in adults, even at an advanced age, without intervening stenosis. There is reason to believe that this occurs in adults, including those in advanced middle life, more frequently than is ordinarily suspected.

That pure mitral insufficiency would be of more frequent occurrence in pediatric practice because of the shorter duration of the process and death during the early stages of the active rheumatic infection has already been mentioned. Thus Sprague and White [8] state: "It is just at this age period of five to 12 years that organic mitral regurgitation is most common." These authors, however, do not refer to the condition as pure mitral regurgitation, unaccompanied by stenosis. Bass [11] believed that one-third of the cases of mitral insufficiency in children are probably unaccompanied by stenosis. Poynton and Paine,[12] in a necropsy series of 150 cases of rheumatic heart disease under the age of 12, found that a marked degree of mitral stenosis was rare, and in 11 cases marked mitral regurgitation was found. Detecting a diastolic murmur at the apex during the course of an active rheumatic process does not necessarily indicate the presence of organic stenosis. In such circumstances the diastolic murmur may be functional, being due to only "relative" stenosis caused by myocardial weakness and ventricular dilatation attendant upon active rheumatic process. The stretching of the mitral ring may not be commensurate with the degree of enlargement of the left ventricular chamber.[6]

In connection with the above recorded observations two questions arise: Is the clinical diagnosis of isolated and pure mitral insufficiency of any practical importance? and, Is such a diagnosis possible on clinical grounds?

With the recent advances made in cardiac surgery, it appears that not only stenosis of the mitral valve but also insufficiency perhaps may be successfully attacked, even though to the present date mitral valve commissurotomy is the operation exclusively performed in most medical centers. However, Bailey, Glover and O'Neill [13] have operated on a few patients in whom, in addition to mitral valve commissurotomy, a pedicle flap of pericardial tissue was attached to the valve, acting as a flap valve and thus correcting the coexistent insufficiency.

Can the diagnosis of pure mitral insufficiency be made clinically? The criteria for the diagnosis of this lesion, as set forth by the New York Heart Association,[14] require the presence of enlargement of the heart in addition to

a systolic murmur at the apex. Scherf and Boyd [3] feel that, in the presence of a systolic apical murmur alone, mitral regurgitation should be diagnosed only if the left auricle is enlarged. Sprague and White [8] are of the same opinion and in addition, they point out that mitral regurgitation causes a general enlargement of the heart, as contrasted with the right ventricular and left auricular enlargement observed with mitral stenosis. It has been said that the giant auricles are related predominantly to regurgitation rather than to stenosis.[15] The left ventricle is not apt to enlarge as much in the presence of mitral stenosis as it does with the deformity of the valve predominantly leading to regurgitation. In the presence of a tight stenosis, the left ventricle may remain practically unaffected when the right ventricle and the left auricle become greatly enlarged. On the other hand, Miller and Wedum [16] are of the opinion that the diagnosis of mitral insufficiency can be made in the presence of the "characteristic" murmur, and that the cardiac enlargement need not necessarily be present. This conclusion rests on their study of a large group of children "with such a murmur" who later showed further signs of valvular damage much more often than children with only potential rheumatic heart disease. It is difficult for us to see pathognomonic characteristics in this murmur, particularly when the authors point out that, in their experience, this murmur "need not be as loud; its intensity may be as faint as that of the diastolic murmur of early aortic insufficiency." Perhaps this may be true in pediatric practice, with which we have no experience, but we do not feel that this stand is applicable in the case of adults. It may be significant that the cardiac surgeons nowadays tell us about their inability to detect the impact of a regurgitant column of blood through the mitral valve in some patients with a clinical diagnosis of mitral insufficiency complicating stenosis on the basis of a well pronounced systolic murmur heard at the apex.

Scherf and Boyd [3] list the following customary auscultatory criteria for distinguishing organic mitral insufficiency from functional apical systolic murmurs: (1) absence of the first sound at the apex; (2) accentuation of pulmonic second sound; (3) transmission of the apical systolic murmur to the lung bases; (4) increased intensity of the murmur with the patient in recumbent position. They criticize these criteria as inadequate in that the absence of the first sound at the apex is an unreliable sign, since mitral regurgitation is usually accompanied by mitral stenosis which accentuates the first sound; that accentuation of the second pulmonic sound is unreliable, since it is absent in early stages and is likewise absent in late stages when right ventricular failure appears; that transmission of the murmur to the lung bases is also of questionable value; and that functional murmurs sometimes bear the same relationship to recumbency as the organic ones.

We both agree and disagree with the above statements. For example, two of our patients had an accentuated second pulmonic sound while in right heart failure. We agree, however, that if the above criteria are too strictly

adhered to, some cases will be missed. On the other hand, when some of these signs are present, they materially aid in the diagnosis. At this point we will take up the problem of the mode of transmission of the murmur in question.

On the basis of our own (although very limited) experience, we feel that transmission of the apical systolic murmur to the back is of considerable diagnostic aid. This murmur is heard characteristically not only at the lung bases but also along the spine as far down as the sacrum. The opinion of some cardiologists that such transmission, presumably along the course of the aorta, is significant of aortic or subaortic stenosis, is an erroneous concept. Rather, mitral origin of such a murmur is to be suspected. Here we agree with the dictum of Baker, Sprague and White [17] that a mitral regurgitant murmur is often well heard at the lung bases. However, we take issue with the same authors relative to other distinguishing characteristics they mention in the following statement: "An interesting and important observation is that some cases originally diagnosed as having mitral regurgitation because of a loud apical systolic murmur were later found to have aortic stenosis. . . . The clue to these cases lies in the fact that the loud, somewhat harsh systolic murmur heard at the apex is also heard at the aortic valve area, although perhaps less loudly. The murmur is primarily an aortic systolic murmur well transmitted to the apex as well as into the neck vessels; a mitral regurgitant murmur is often well heard at the lung bases (and in the left axilla), but not at the aortic valve area." Not only was the murmur in our patients well heard in the aortic area, but in one case it was also transmitted into the neck vessels. None of our patients had deformity of the aortic valve or of any other than the mitral valve. That systolic murmurs originating at the mitral opening can be transmitted to the carotid arteries, as is known to occur in the case of the systolic murmur of aortic stenosis, had been noted also by others. Thus, Rytand and Lipsitch [18] record this finding in their patients with calcified mitral annulus fibrosus, who had normal aortic, pulmonic and tricuspid valves at necropsy. In a way this seems to bear out the stand of Levine,[5] who questions the diagnostic importance frequently attached to transmission of murmurs. He demonstrated that murmurs were not necessarily propagated with the blood stream; for example, he was able to detect the murmur over the olecranon process, even with the blood pressure cuff inflated above the systolic pressure level.[19] However, we are so impressed with our findings that in this diagnosis of organic mitral insufficiency we are inclined to uphold the significance of wide transmission of the murmur not only to the bases but also along the spine as far down as the sacrum.

The symballophone may be of assistance in localizing the true origin of the sound. This instrument is a special stethoscope devised for comparison and lateralization of the sound, which may enable one to determine the point of origin of the murmur and to note its direction.[20, 21]

Our patients had a loud, harsh systolic murmur, heard over the entire precordium, including the aortic area, with maximal intensity over the apex, and radiation to the axillae, lung bases and along the spine as far down as the sacrum. The murmur is sometimes holocustic and holosystolic in its propagation and duration. It may be transmitted to the neck vessels (in the absence of deformity of any valve other than the mitral). The murmur, in our experience, is usually accompanied by a well pronounced systolic thrill at the apex.* Three patients had auricular fibrillation and one sinus rhythm. All patients had marked cardiac enlargement, consisting principally of left auricular and ventricular enlargements. In only one case was there electrocardiographic evidence of right ventricular hypertrophy. There was no definite electrocardiographic evidence of left ventricular hypertrophy in any of them. All patients were in congestive heart failure.

We feel that, even in the absence of a history of rheumatic fever, a harsh and fairly loud systolic murmur at the apex, also heard at the lung bases and along the entire spine, with or without an accompanying thrill, in combination with left auricular and ventricular enlargement, all constitute in adults a constellation of signs practically pathognomonic of organic mitral regurgitation. This, however, does not absolutely and unequivocally make a diagnosis of pure mitral regurgitation, as occasionally the diastolic murmur of mitral stenosis is not heard in the presence of the stenotic lesion of the mitral valve. But at least a strong suspicion of pure mitral regurgitation may be legitimately entertained.

The murmur of mitral insufficiency of rheumatic origin as above described must be differentiated from other conditions producing it, such as calcification of the mitral annulus fibrosus, ruptured mitral chordae tendineae, occluding thrombus of the right auricle, congenital malformations and trauma. Calcification of the annulus fibrosus of the mitral valve is in itself clinically unimportant, although it may give rise to a loud, rough, apical systolic murmur. Calcification may be detected on fluoroscopic examination. When associated with pathologic changes in the septum, heart block may develop. Heart failure or anginal syndrome, when present, is due to associated cardiovascular disease, such as hypertensive heart disease, "presbycardia" or coronary artery disease, and is not to be attributed to the direct effects of the calcium deposits. However, it is possible that calcification of the mitral ring may interfere with the systolic diminution inside the mitral orifice and thus favor regurgitation.[17] Rytand and Lipsitch,[18] as a result of a study of 10 such cases (of which three came to necropsy), arrived at the conclusion that the murmurs would not be regarded as evidence of either mitral regurgitation or stenosis. Occluding thrombus of the left auricle may occur on the substratum of mitral stenosis or degenerative type

*We now have in the hospital a patient who is believed to have pure and isolated mitral insufficiency, with a systolic thrill not only at the apex but also over the pulmonic area. Of course, we have here no anatomic proof of the suspected diagnosis.

of heart disease, and it is to be suspected on the basis of the sudden and transitory appearance of peripheral vascular disturbances.[23] Death takes place shortly after the appearance of these disturbances. The diagnosis of the rupture of mitral chordae tendineae is attendant upon the diagnosis of the causative conditions of myocardial infarction, bacterial endocarditis and trauma, and is of particularly rare occurrence in the last mentioned instance.[24] Congenital malformations are extremely rare.

Fluoroscopy may aid in the diagnosis of mitral insufficiency by demonstrating expansile pulsations of the left auricle occurring synchronously with the inward (systolic) movement of the ventricular border.[25] This again, however, does not establish the diagnosis of pure mitral insufficiency, as some degree of stenosis may still allow considerable regurgitation of blood in systole.

Circulatory dynamics in pure mitral insufficiency have hardly been investigated. Recognition of this condition during life would lead to possibly fruitful investigations of this type of circulatory disturbance by the procedure of cardiac catheterization. In fact, Dexter and co-workers [4] have carried out such a study in one patient suspected of having pure mitral regurgitation of the congenital type.

Summary

In the group of 44 autopsied cases of rheumatic heart disease we found four cases of pure and isolated mitral valve incompetence without deformity of any other valve, pericarditis, hypertension, coronary artery disease, syphilis or any other type of cardiac involvement except rheumatic (with the exception of bacterial endocarditis in one instance). All four patients died in congestive heart failure at the ages of 42, 50, 51 and 56, respectively. Thus, all four patients apparently died of no cause other than those secondary to pure mitral valve incompetence.

Modern standard texts and reference works on cardiology, as well as the current literature, create the impression that, in adults, fatalities from heart failure occur but rarely during the stage of pure mitral insufficiency. The evidence here presented tends to show that such an impression is probably incorrect, and that death from this cause may well occur in adults, even in advanced middle life, more frequently than is currently believed.

The diagnostic features of pure and isolated mitral insufficiency are discussed. In passing, a note can be made of the fact that sclerosis of the pulmonary vasculature seen in some patients with mitral stenosis was not observed in our cases of pure mitral insufficiency.

BIBLIOGRAPHY

1. Lewis, T.: Diseases of the heart, 1933, Macmillan Company, New York.
2. White, P. D.: Heart disease, 3d Ed., 1944, Macmillan Company, New York.
3. Scherf, D., and Boyd, L. J.: Cardiovascular diseases, 1947, J. B. Lippincott Company, Philadelphia.

4. Gorlin, R., Lewis, B. M., Haynes, F. W., and Dexter, L.: Studies of the circulatory dynamics at rest in mitral valvular regurgitation with and without stenosis, Am. Heart J. **43**: 357, 1952.
5. Levine, S. A.: Clinical heart disease, 4th Ed., 1951, W. B. Saunders Company, Philadelphia.
6. Bland, E. F., White, P. D., and Jones, T. D.: The development of mitral stenosis in young people, Am. Heart J. **10**: 995, 1934–1935.
7. Friedberg, C. K.: Diseases of the heart, 1949, W. B. Saunders Company, Philadelphia.
8. Sprague, H. B., and White, P. D.: A comparative study of "rheumatic" mitral regurgitation and mitral stenosis, Am. Heart J. **1**: 629, 1926.
9. Dana, H. W., and Reidy, J. A.: Mitral valve disease. Pathologic report, Am. J. M. Sc. **191**: 109, 1936.
10. Cabot, R. C.: Facts on the heart, 1926, W. B. Saunders Company, Philadelphia.
11. Bass, M. H.: Abt's pediatrics, IV, 1924, W. B. Saunders Company, Philadelphia.
12. Poynton, F. J., and Paine, A.: Researches on rheumatism, 1913, Macmillan Company, New York.
13. Bailey, C. P., Glover, R. P., and O'Neill, T. J. E.: Closed intracardiac tactile surgery, Dis. of Chest **12**: 1, 1952.
14. Nomenclature and Criteria for Diagnosis of Diseases of the Heart, 4th Ed., New York Heart Association, New York, New York Tuberculosis and Health Association, 1939.
15. Cabot Case No. 38231, New England J. Med. **246**: 906, 1952.
16. Miller, J., and Wedum, B. G.: Cardiac enlargement in uncomplicated mitral insufficiency in children, Am. J. Dis. Child. **78**: 703, 1949.
17. Baker, L., Sprague, H. B., and White, P. D.: The clinical significance of loud aortic and apical systolic heart murmurs without diastolic murmurs, Am. J. M. Sc. **206**: 31, 1943.
18. Rytand, D. A., and Lipsitch, L. S.: Clinical aspects of calcification of the mitral annulus fibrosus, Arch. Int. Med. **78**: 544, 1946.
19. Levine, S. A.: Some notes on the transmission of heart murmurs, Ann. Int. Med. **21**: 298, 1944.
20. Kerr, W. J., Althausen, T. L., Bassett, A. M., and Goldman, M. J.: The symballophone: a modified stethoscope for the lateralization and comparison of sounds, Am. Heart J. **14**: 594, 1937.
21. Kerr, W. J.: The clinical use of the symballophone, West. J. Surg. **49**: 632 (Nov.) 1941.
22. Fishberg, A. M.: Heart failure, 2nd Ed., 1940, Lea and Febiger, Philadelphia.
23. Schwartz, S. P., and Biloon, S.: The clinical signs of occluding thrombi of the left auricle, Am. Heart J. **7**: 84, 1931–1932.
24. Frothingham, C., and Haas, G. M.: Rupture of normal chordae tendineae of mitral valve, Am. Heart J. **9**: 492, 1934.
25. Elkin, M., Sosman, M. C., Harken, D. E., and Dexter, L.: Systolic expansion of the left auricle in mitral regurgitation, New England J. Med. **246**: 958, 1952.

EXPERIENCES IN THE DIAGNOSIS AND ANTIBIOTIC THERAPY OF AMEBIASIS: AN ANALYSIS OF 50 CASES *

By Nelson J. Weiser, Captain, MC, AUS, *New York, N. Y.*, Eugene Spiotta, 1st Lieut., MC, AUS, *Fort Campbell, Kentucky*, and Pierre Ekman, 1st Lieut., MSC, AUS, *Hapeville, Georgia*

Statement of Purpose

At an Army installation drawing much of its patient population from veterans of the Korean war, we have had the opportunity to observe 50 patients with amebiasis. These patients demonstrate the wide variations in the manifestations of this disease, including some which have seldom been reported. They illustrate the difficulties encountered in diagnosis and the frequency with which patients with amebiasis are thought to have a surgical abdominal emergency. We have had an almost unique opportunity for prolonged, close and intensive observation of these patients, one seldom found in private practice, and we have had therapeutic results at variance with those reported in the recent literature. For these reasons and because there is likely to be increased incidence of this disease among soldiers returning from the Far East, we submit this paper.

Procedure

The diagnosis was made in suspected patients by sigmoidoscopy, with examination of the mucus obtained on mucosal swabs, or by stool examination. Stools were obtained by purging in all patients in whom we had clinical reason to suspect amebiasis, but were casual specimens in the routine examination of food handlers. They were immediately examined by direct smear and by zinc flotation technics. Sigmoidoscopy was done on all patients found positive on stool examination, and on all patients in whom the clinical suspicion of amebiasis arose. Our index of suspicion was high and chiefly embraced (1) all patients who gave a history of chronic or recurrent diarrhea, or of frequent soft, mushy stools, regardless of environmental contact; (2) those who complained of frequent abdominal pain or flatulence for which no other adequate cause could be found; (3) patients (such as food handlers) who on routine stool examination were found to have parasites of any kind; (4) patients with recurrent episodes of hepatitis, particularly atypical hepatitis; and (5) patients who gave a history of amebiasis, even if they had been treated and were now asymptomatic. The swabs obtained at sigmoidoscopy were examined directly and by D'Antoni's iodine

* Received for publication November 28, 1952.
From the Medical Service, U. S. Army Hospital, Fort Campbell, Kentucky.

technic for trophozoites and cysts, and all results were confirmed by smears of the same material stained with iron hematoxylin.

While under therapy the patients were sigmoidoscoped at intervals, and the above diagnostic procedures were repeated in an attempt to evaluate response to therapy.

We found sigmoidoscopy vastly superior to careful stool examination in the diagnosis of the disease (table 1). (Only 39 of our 50 patients are included in this table, as the remaining 11 did not have stool examinations prior to therapy.)

TABLE I

Number of Patients	Sigmoid +, Stool +	Sigmoid +, Stool −	Sigmoid −, Stool +
39	4	30	5

Because of the greater reliability of sigmoidoscopy with direct examination of the mucosal aspirate in diagnosing the presence of *Endamoeba histolytica*, we believe this procedure with a negative result to be one of the essential criteria of cure.

INCIDENCE AND EPIDEMIOLOGY

Most and his associates estimate the incidence of all forms of amebiasis, including asymptomatic cyst passers, to be 10 per cent for the U. S. population as a whole, 5 to 15 per cent for Pacific veterans, and 4 per cent for all veterans. Local variations are reported to be as wide as from 1 to 40 per cent.[1] Faust points out that most surveys have been of a single stool specimen, and believes that 20 per cent of the United States population may be infected.[68] It is clear that, as in the case of tuberculosis, every infected individual is potentially ill with the disease but only a relatively small number of persons are sufficiently symptomatic to seek medical care. However, every asymptomatic carrier of *E. histolytica* is a potential source of infection for others. The problem of infectiousness will continue to grow as our troops return from the Far East. After the last war, Jacobs estimates that 20 per cent of the troops returning from the China-Burma-India theater were parasitized, compared with 10 per cent of troops with no overseas service.[59] Radke found *E. histolytica* in 47 of 93 Korean veterans.

Infection is acquired by the ingestion of food or drinking water containing the cysts of *E. histolytica* and is therefore a function of poor sanitation. It may be carried by flies to previously uncontaminated food.

PATHOGENESIS AND PATHOLOGY

The action of *E. histolytica* is the same in all susceptible animals.[49] Upon reaching the small bowel the cyst gives way to the vegetative form (trophozoite). This secretes a histolytic toxin which produces a break in the intestinal mucosa through which the trophozoite migrates. Alternatively,

trophozoites may enter the lumen of a mucosal gland before producing lysis deep within the fundus of the gland. Here they cause edema with dilatation and thrombosis of capillaries; necrosis and further ischemic tissue destruction result. The muscularis is a relative but not an absolute barrier.[49] If the amebic ulcer does not invade the muscularis, it spreads laterally with the muscularis as its base to produce the characteristic, basally communicating Erlenmeyer flask ulcer. Host cellular reaction is slight unless there is secondary bacterial invasion. The muscularis may be involved by hyalinization followed by necrosis. Local or generalized peritoneal perforation may rarely occur. Some of the trophozoites enter lymphatics and venules and are carried to the liver to produce the hepatic complications to be discussed. Sites of intestinal preference for the described changes are listed in table 2.

TABLE II

Ileum	5.6%	Asc. colon and hepatic flexure	8.4%
Ileocecal valve	2.4%	Transverse colon	4.4%
Cecum	33.3%	Splenic flexure and desc. colon	6.4%
Appendix	32.1%	Sigmoid colon	12.9%
		Rectum 15.7%	

On proctoscopic examination these processes manifest themselves early as raised spots of hyperemia (the early, invasive phase), followed by a shallow ulcer with a narrow, hyperemic ring; then a diffusely granular mucosa (lymphoid hyperplasia, which may be related to secondary infection), followed by nodular, sharply circumscribed projections of mucosa with small, depressed yellow openings and surrounded by narrow rings of hyperemia.[49] Chang found the ulcers to assume no characteristic appearance. He found the intervening mucosa normal in 21 patients, pale in 12 and edematous in 39.[29] In our proctoscopies we have been impressed with the frequency of copious amounts of viscid, water-clear or greenish mucus overlying a normal or slightly hyperemic mucous membrane; such mucus was usually loaded with *E. histolytica* trophozoites. We believe this to indicate infection above the reach of the instrument in patients with uninvolved rectosigmoid colons.

Complications are local and distant. In the colon, in addition to perforation as already described, there may be ameboma formation, pseudopolyposis and/or cicatrization. Amebomas are formed anywhere, and are composed of granulation tissue which may encircle the bowel. They are characterized microscopically by round cell and eosinophilic infiltration and lymphoid hyperplasia.[30]

Pseudopolyposis probably occurs only in chronic cases, although we have seen a patient (see case 5, reported below) with a history of recent onset. In our search of the literature we found only two isolated case reports.[31, 32] On pathologic examination these lesions prove to be pseudopolyps and not true adenomata.

The incidence of hepatitis in autopsied cases of amebiasis can be determined more or less accurately, but the incidence reported in clinical cases

will depend largely on the author's criteria for the diagnosis of amebiasis. Klatskin found liver involvement in 36.6 per cent of a large series of autopsy cases collected from the literature, but only 4.9 per cent involvement in a large series of clinical cases similarly collected. Payne reported liver involvement in 56.7 per cent of 100 cases of clinical dysentery.[8] Obviously, if every cyst passer is considered a case of amebiasis, the incidence of liver involvement is extremely low; on the other hand, a falsely low percentage involvement may be suggested to the investigator who is not alert to the nonspecific and low grade signs of hepatic amebiasis. Amebic liver abscess occurs predominantly in males. Ochsner and DeBakey report 85 per cent males in 139 personally observed cases, and 95.3 per cent males in 1,487 cases in the literature.[39] Councilman and Lefleur report 21 per cent amebic abscesses among their series of cases of nonfatal amebic dysentery. In 19 autopsied patients, all of whom died of amebiasis, Palmer reports 13 patients with abscess. Twelve of these had involvement of the right lobe and five were multiple. Clinically, before death, 12 had hepatomegaly and six had leukocytosis. At autopsy, the six patients who did not have abscess had amebic hepatitis without abscess. Changes other than abscess included increase in portal connective tissue, which was irregular in distribution and amount, bile duct proliferation, and compression of liver parenchyma in the neighborhood of abscesses.[9]

Other authors report multiple abscesses in 25 to 66 per cent of autopsy cases. Ochsner and DeBakey found single abscesses in 89 per cent of clinical and autopsy cases, the majority of which were clinical. They state that "left lobe involvement occurs so infrequently that it is considered report-worthy." Out of 2,179 collected cases of single abscess, 84.6 per cent were in the right lobe. The authors' series of 139 cases were 96.3 per cent in the right lobe and 3.6 per cent in the left lobe.[46]

Klatskin classifies amebic liver involvement as acute, subacute and chronic amebic hepatitis, and as acute and chronic liver abscess.[45] There are three conceivable routes of liver infestation: (1) by direct extension—bowel wall to peritoneum to liver capsule; (2) via lymphatics, and (3) via the portal vein. Of these, the third is by far the most important. In the stage of hepatitis the picture is one of cytolyzed liver cells, red cells, fibroblasts and occasional parasites, occurring chiefly in the portal zones.[46] If abscesses do not form and the process is progressive, this terminates in an irregularly scarred liver, as described by Palmer.

The earliest stage of the small, acute abscess is thrombosis of the small portal radicle, followed by necrosis of the adjacent liver parenchyma due to anoxia and the cytolytic action of the parasite. There the process may become dormant, or the trophozoites may spread along the contiguous venules, producing more necrosis and a larger abscess cavity with minimal reaction around it. In the end stages the wall becomes organized and a connective tissue capsule forms about the abscess. The surrounding paren-

chyma is compressed. Unless there is secondary infection there are very few inflammatory cells. In uncomplicated cases the abscess contents are chocolate sauce in color; with secondary infection they become purulent.[49, 50, 9] The amebae are found in the necrotic zone adjacent to the fibrous capsule of the abscess, but they are seldom found in older abscesses with thick capsules. Hence it is difficult to demonstrate amebae in surgically opened abscesses, although they may appear days later in the drainage. Rogers et al. have scraped the abscess wall at the time of open drainage and have found the scrapings positive for *E. histolytica* in 65 to 95 per cent. Ochsner and DeBakey did not scrape the wall and found only 16.5 per cent positive on direct examination of the pus.[46]

Payne in India found the following incidence of complications in 1,000 cases of amebiasis, not necessarily with dysentery:

Mild hepatitis, 50 per cent; severe hepatitis, 3.9 per cent; hepatic abscess, 2.8 per cent; severe hemorrhage, 0.2 per cent; local peritonitis, 1.0 per cent; perforation, 0.8 per cent; rectal granuloma, 0.2 per cent.[8]

Symptoms and Signs

We wish to emphasize again what has been mentioned by the great majority of those who have dealt with large series of patients with amebiasis; that true dysentery, by which we mean tenesmus, diarrhea and abdominal cramps, occurs in a minority of patients. A breakdown of the symptoms noted in our series is seen in table 3.

Table III

I. Abdominal pain	80% of all patients
Right lower quadrant	28%
Both lower quadrants	36%
Left lower quadrant	4%
Right upper quadrant	10%
Epigastrium (mid)	2%
II. Diarrhea	48% of all patients
(A) Mucoid	40%
Watery	8%
(B) Recurrent	40% of all patients with diarrhea
Continuous	58% of all patients with diarrhea
Alternating with constipation	2% of all patients with diarrhea
III. Nausea and Vomiting	28% of all patients
IV. Flatus (Excessive)	34% of all patients
V. No Symptoms	6% of all patients

. It is clear that a patient complaining of only a rather nonspecific type of lower abdominal pain, in the absence of physical findings, will ordinarily not be subjected to sigmoidoscopy or examination of mucosal aspirate taken at the time of this examination.

Case Reports

Case 1. From 1945 to 1948 this 35 year old Army captain served in New Guinea, Guam and Okinawa. While there he had several episodes of diarrhea which sub-

sided without investigation. These symptoms were so widespread among the troops that he did not report for medical attention. From 1948 to 1952 he repeatedly reported to dispensaries complaining of dull, continuous bilateral lower quadrant pain and the passage of excessive amounts of flatus. These were his only complaints; diarrhea did not recur following his return from the Pacific. Gall-bladder and gastrointestinal x-rays were repeatedly negative. In January, 1952, the diagnosis of amebiasis was established by sigmoidoscopy.

Clearly it would not be sufficiently productive in the general population to sigmoidoscope every patient with such nonspecific symptoms. We believe, however, that every veteran of the Pacific theater of operations should be suspected of having some form of intestinal parasite when he complains of vague, nonspecific gastrointestinal disorders. Study should include stools and proctoscopic examination for intestinal parasites.

D'Antoni classifies the symptoms of amebiasis as follows:

I: Asymptomatic amebiasis
II: Symptomatic amebiasis
- A. Asyndromic: mild toxemia; vague gastrointestinal complaints.
- B. Syndromic: lesions generally in the cecal area.
- C. Dysenteric.
- D. Hepatitis and/or liver abscess.
- E. Involvement of other organs.

We shall not describe all these symptom complexes in detail. However, we are struck with the frequency with which these patients have as their only symptom recurrent bouts of right lower quadrant pain (D'Antoni's "syndromic" group). Several of our patients had previously been operated on either here or at another hospital.

Case 2. A 24 year old white male had gnawing right lower quadrant pain beginning five weeks before admission, which was particularly severe when he walked rapidly or rode in a car. Twelve hours before admission the pain became much more severe. Examination revealed guarding without spasm and rebound tenderness over McBurney's point. The temperature was normal. A grossly and histologically normal appendix was removed. Postoperatively the pain persisted. Sigmoidoscopy demonstrated *E. histolytica.*

Case 3. A 19 year old white male developed dull, constant right lower quadrant pain in April, 1951. In June, a normal appendix was removed. Pain persisted, and two months postoperatively fever developed. Genitourinary workup was negative. In October he was transferred to the medical service and the diagnosis of amebiasis was made on sigmoidoscopy. Antiamebic treatment caused remission of fever and pain for the first time since April.

Case 4. A 25 year old white male developed severe right lower quadrant pain in 1949 and was told he had gall-bladder disease. The pain recurred several times, several diagnoses were made, and an appendectomy was done, with no relief. Later a laparotomy was done and "adhesions" were released, again with no relief. Pain was severe when the patient rode in a car or bus. Physical examination revealed tenderness in the right lower quadrant but was otherwise negative. In January, 1952, sigmoidoscopy revealed trophozoites of *E. histolytica.* The patient has been free of pain since antiamebic therapy was given seven months ago.

The appendices in cases 2 and 3 were removed at this installation and were reëxamined after the diagnosis of amebiasis was made. They were negative histologically and showed no parasites. Others have occasionally found amebae in otherwise normal appendices in such patients. In Payne's series of patients with right lower quadrant pain as their only complaint he found the white count to be 10,000 to 14,000, usually with a normal differential. The temperature was usually normal, and the diarrhea and mucus characteristic of "dysenteric" patients were seldom observed. One-third of his patients were negative for *E. histolytica* on initial stool examination.[8] In our experience, these patients often developed right lower quadrant pain after an automobile ride or after the jarring consequent to running or jumping. In New Orleans Charity Hospital (an endemic area), 10 per cent of patients diagnosed as having "chronic appendicitis" were found to have *E. histolytica* in their stools, and their symptoms cleared on antiamebic therapy.[39] D'Antoni correlates bouts of right lower quadrant pain with cecal lesions, and diarrhea with rectosigmoidal lesions.[39]

Ochsner and DeBakey state that appendicitis as an acute suppurative or a chronic inflammatory process is a frequent complication of amebiasis, and that it is responsible for death in 7 to 40 per cent of the fatal cases collected from the literature.[30] On the other hand, Payne states that he has seen no amebic appendicitis in 2,000 cases of intestinal amebiasis.[8]

Ameboma may cause obstructive symptoms and may in some cases coexist with or be indistinguishable from carcinoma clinically and roentgenologically.[5] However, Palmer reports a patient who had symptoms of colitis and who showed two constricting lesions in the transverse colon radiologically which were distinguished from carcinoma by their smoothness and by the absence of mucosal irregularity. They responded to medical therapy.

Pseudopolyposis has been associated with chronicity; the symptoms are otherwise those of colitis generally. Rare case reports in the literature have already been referred to. We have had a case of our own.

Case 5. In August, 1951, while on maneuvers in North Carolina, this 24 year old white male developed abruptly a watery diarrhea, fever, tenesmus and colicky abdominal pain. No prior history of gastrointestinal disease was obtained except for "worms" as a child. During the next six weeks he developed electrocardiographic evidence of hypokalemia, weight loss and dehydration. In September he arrived here chronically ill and emaciated. Sigmoidoscopy prior to his arrival was reported as showing a friable mucous membrane.

Our first sigmoidoscopy revealed a hyperemic mucous membrane but was otherwise negative. Examination for *E. histolytica* was not done on this occasion. Biopsy of the mucous membrane revealed edema and lymphocytic infiltration. Barium enema (figure 1) revealed what appeared to be small adenomatous polyps throughout the entire colon except for the sigmoid area. The radiologist rejected our clinical impression of nonspecific ulcerative colitis because of the preservation of haustral markings and the absence of spasm and cicatricial narrowing of the bowel lumen. These findings were thought inconsistent with the pseudopolypoid stage of idiopathic

Fig. 1

Fig. 2

FIG. 1. September, 1951. Acutely ill. Fair preservation of haustral markings and bowel lumen. Pseudopolyposis.
FIG. 2. October, 1951. In remission. Good haustral markings; normal bowel caliber. Pseudopolypi.

ulcerative colitis, and the radiologic diagnosis was congenital polyposis. We felt the latter impression was inconsistent with clinical findings, namely, the absence of polypi in the lowest 25 cm., where they would ordinarily be most numerous, the lack of a history of rectal bleeding during the first 24 years of the patient's life, and the lack of a family history of polyposis. We repeated sigmoidoscopy to confirm the absence of polyps in the lower bowel. We found the lowest 25 cm. normal on this occasion except for the presence of copious opalescent mucus containing the trophozoites of *E. histolytica*. The patient was treated for amebiasis, with clinical improvement and with diminution of the number of "polyps" demonstrable on x-ray (figure 2). Later there was marked deterioration of his clinical condition, and in time the sigmoidoscopic picture became and remained indistinguishable from that of chronic ulcerative colitis. It was marked by ulceration, bleeding, spasm, pseudopolyposis and friability with copious mucus. The mucus was alternately positive and negative for *E. histolytica*, but recent examinations have been negative. The picture reflected his clinical condition (figures 3 and 4), and it is now radiologically indistinguishable from the picture of chronic nonspecific ulcerative colitis.

To summarize, this very interesting patient presented a radiologic picture of pseudopolyposis while in his acute stage of dysentery (compare previous reports of pseudopolyposis only with chronic disease), and progressed inexorably (although with temporary remissions) to the clinical, sigmoidoscopic and radiologic picture of chronic ulcerative colitis. We feel that it is impossible to say whether his amebiasis played a major rôle, a minor rôle or no rôle in the development of his final picture. Palmer reports that three out of 40 of his patients developed ulcerative colitis within two months of a parasitologic cure of their amebiasis.[35] The relationship between amebiasis and ulcerative colitis might bear re-investigation.

The important clinical complications of amebiasis, so far as the intestine is concerned, are listed by Ochsner and DeBakey as follows:

Appendicitis	(7 to 40 per cent of collected fatal cases)
Perforation	(4 to 19 per cent of fatal cases; 1.5 per cent of clinical cases)
Hemorrhage	
Ameboma	
Cicatricial stenosis	
Pseudopolyposis	

The most important extraintestinal complications are those involving the liver. Others have observed, as we have, that a history of intestinal symptoms cannot be depended on in directing one's attention to hepatic amebiasis. Ochsner and DeBakey state: "In from one-third to almost one-half the cases of amebiasis of the liver the history of an antecedent diarrhea will not be obtained."[46] Klatskin noted a history of dysentery in 13 per cent and of intermittent diarrhea in 63 per cent of his cases of amebic hepatitis and hepatic abscess, and he found that the interval between infection and hepatic symptoms varied from one week to 20 months, with an average of six months.[45] The same author quotes Rogers' series of autopsy cases of amebic infestation of the liver in which 77.8 per cent had active dysentery and 20 per cent had the scars of healed dysentery. It may be assumed that in cases

Fig. 3

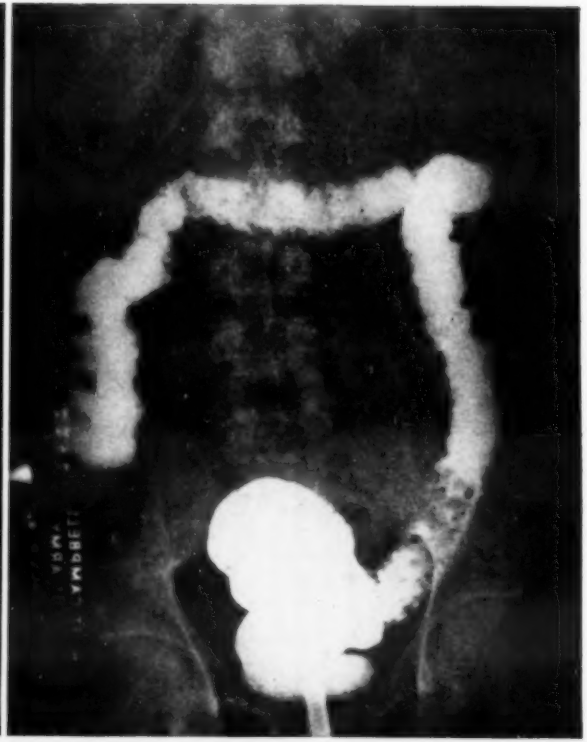


Fig. 4

FIG. 3. November, 1951. Early relapse. Definite increase in pseudopolyposis, but haustral markings are preserved and caliber is normal.

FIG. 4. March, 1952. Severe relapse. Clinical picture of advanced, active ulcerative colitis. Haustral markings are lost and bowel caliber is reduced.

not severe enough to come to postmortem the incidence and severity of intestinal lesions will be lower. Ochsner and DeBakey found the interval between intestinal and hepatic symptoms to be as long as six to eight years in some patients and noted that a 43 year interval has been recorded.[46] The possibility of re-infection or superinfection must be kept in mind, however.

The onset of symptoms in hepatic amebiasis may be acute or insidious. Klatskin noted symptoms in his series as shown in table 4.[45]

TABLE IV

	Abscess	Acute Hepatitis	Subacute Hepatitis	Chronic Hepatitis
Symptoms				
Pain	100%	90%	55%	100%
Fever	100	100	60	30
Diarrhea	15	50	80	75
Nausea, vomiting	30	60	20	30
Signs				
Subcostal tenderness	85%	85%	100%	100%
Liver enlarged	70	68	80	100
Compression tenderness	100	75	80	100
Abnormal lung findings	70	35	15	15

In contrast to viral hepatitis, hepatic amebiasis is marked by a disproportion between signs and symptoms on the one hand and the laboratory abnormalities on the other. Only 12 per cent of Sodeman's patients with acute amebic hepatitis were jaundiced, and the cephalin flocculation and thymol turbidity tests were not consistently abnormal.[17] In 23 cases of amebic hepatitis, Sodeman and Lewis depended for their diagnosis on an elevated diaphragm in nine, on known colonic amebiasis in 11, and on a positive complement fixation test in one. All responded to emetine. The following cases of hepatic amebiasis from our series indicate the relatively indefinite basis on which the diagnosis often must rest.

Case 6. A 39 year old white female patient became ill in Germany in January, 1949, with epigastric pain and vomiting. She and her husband disagree on whether jaundice was present, and records are unavailable. A diagnosis of infectious hepatitis was made and she was hospitalized for 51 days. Since that time she has frequently had recurrent fever, right upper quadrant pain, nausea and vomiting. In 1950 she was treated with Atabrine for amebic colitis. She has been hospitalized four times for these gastrointestinal complaints and on no occasion has she been jaundiced again. In addition, she has been treated at home on many occasions for anorexia, nausea and elevations in temperature for which no cause was found. The patient gave a history of excessive alcohol intake while in Germany but not since 1949. Her present episode began two days prior to admission with nausea, fever, vomiting and right upper quadrant pain. On admission the patient complained bitterly of right upper quadrant pain, and retched repeatedly. The liver was felt four fingerbreadths below the right costal margin and was exquisitely tender. Her temperature was normal on admission and never rose to 100° F. throughout her subsequent hospital course. However, white blood counts ranged from 20,000 to 27,000, with a shift to the left during the first week

of hospitalization. Gastrointestinal and gall-bladder series were both normal. Liver function studies were normal. On proctoscopy excessive viscid, watery mucus was found, and the trophozoites of *E. histolytica* were readily found in direct smears of the mucus.

Case 7. A 40 year old white male who served in China during World War II was admitted to this hospital January 21, 1952, complaining of right upper quadrant pain of 10 days' duration. The pain initially had occurred only intermittently after exercise or jarring. Gradually it became more severe, until inspiration or coughing produced excruciating pain. He denied symptoms referable to the gastrointestinal, respiratory or biliary systems prior to this illness. He had no past or present urinary symptoms. Physical findings included impaired expansion of the right hemithorax and exquisite tenderness of the right upper quadrant of the abdomen, with muscle guarding and rebound tenderness. Admission temperature and white blood cells and differential were normal. Chemical studies, including serum amylase, total protein and A-G ratio, cephalin flocculation, thymol turbidity and alkaline phosphatase, were all normal. Total serum bilirubin was less than 1 mg. per cent. A bromsulfalein test on the fourth day showed 11 per cent retention in 45 minutes.

During the first five days of hospitalization the patient ran a low grade fever, with maximal recordings of 101° F. The abdominal physical findings remained unchanged. The clinical diagnosis of acute cholecystitis was concurred in by the surgical consultant. However, a gall-bladder series done on the eighth hospital day was entirely normal. Symptoms were still present at the time of this examination. Complement fixation tests for amebiasis were positive on January 23 and on February 20. No antiamebic therapy had been given during this interval. By March 1 the symptoms had partially subsided on symptomatic therapy. On this date chloroquine diphosphate and terramycin were begun, after proctoscopy had failed to demonstrate intestinal amebiasis. On antiamebic therapy the patient became and remained asymptomatic.

Case 8. A 22 year old white female patient had been admitted to the hospital in April, 1952, complaining of right upper quadrant pain and low grade fever. On examination at that time the only positive physical findings were right upper quadrant and right costovertebral angle tenderness. No organs were felt. Urinalysis revealed the presence of albumin and pus cell clumps. The patient was treated for pyelitis. A bromsulfalein test taken on admission (because the differential diagnosis was thought to include viral hepatitis without icterus) was reported as showing 22 per cent retention. This result was not supported by other liver function studies and was dismissed as a laboratory error. The patient was discharged asymptomatic on May 8. She returned May 22, stating that since her arrival at home she had continued to have right upper quadrant pain associated with nausea, vomiting and several brief rigors.

On examination the patient was obviously mildly icteric. The abdomen was diffusely tender, tympanitic and distended. There was diffuse muscle guarding, making palpation for organ enlargement impossible. Peristalsis was active. There was punch tenderness at both costal margins anteriorly and in the costovertebral angles. There was pallor of the skin and mucous membranes. Admission blood count revealed white blood cells, 5,400, with a normal differential. A normochromic anemia was present, with a hemoglobin of 9.0 gm. per cent. Total serum bilirubin was 3.4 mg. per cent, and the van den Bergh was biphasic. Cephalin flocculation was 1 plus in 48 hours; thymol turbidity was 15.5 units. Alkaline phosphatase was 9 Bodansky units. Heterophil agglutination was repeatedly normal. Prothrombin level, blood proteins and A/G ratio were normal. Blood cholesterol was 158 mg. per cent, with 80 per cent esters. Reticulocyte counts showed normal percentages. A flat film of the abdomen showed generalized bowel distention down to the rectum; no fluid levels

were seen, and intraperitoneal fluid was also not indicated on this film. A gall-bladder series done while the patient was jaundiced failed to visualize; subsequently, a gall-bladder series was normal. Blood agglutinations for leptospirosis were twice negative, as was blood complement fixation test for amebiasis. Sigmoidoscopy revealed the presence of large amounts of viscid, water clear mucus containing *E. histolytica* trophozoites in large numbers.

The patient's hospital course was characterized by slow progressive improvement on chloroquine, terramycin, high protein diet and vitamin supplements. By July 3 she was asymptomatic. She was allowed home on a weekend pass and failed to return to the hospital.

The first of these patients had recurrent hepatitis with a tender, enlarged liver but with normal liver function studies. The history of alcoholism in the past led the admitting physician to attribute the picture to a postalcoholic fatty infiltration and cirrhosis with superimposed acute hepatitis. The key to the diagnosis was the finding of *E. histolytica* on sigmoidoscopy, a procedure suggested by the past history of amebiasis and the atypical picture. The second patient had an episode of acute right upper quadrant pain, thought to represent biliary disease. His diagnosis depended on our high index of suspicion after biliary tract studies had proved normal. The third patient was proctoscoped because of the presence of an unusual type of hepatitis that did not suggest viral hepatitis (generalized abdominal tenderness, late onset of jaundice, relatively normal liver function studies), or leptospirosis (absence of significant temperature rise or of exposure to rodents), or primary obstructive type of jaundice (afebrile course, age of patient, absence of predisposing factor—later confirmed by gall-bladder studies). The low grade laboratory changes in these patients is in agreement with the experience of others. Dennis states that the incidence of severe hepatitis with leukocytosis in patients with stools positive for *E. histolytica* probably does not exceed 2 per cent of amebiasis patients observed at Beirut. The incidence of hepatic abscess was less than 0.25 per cent of the same series.

The physical findings in Klatskin's series of hepatic amebiasis are detailed in table 4.

Ochsner and DeBakey found both liver pain and fever in 85 per cent of cases of hepatic amebiasis (hepatitis or abscess or both), with enlargement of the liver in over 70 per cent. Ten per cent of their series were jaundiced, the average icterus index among these being 38, and the maximum 200.[46] Sodeman and Lewis found liver pain and fever almost universal, and found jaundice in five of their 33 patients. Diarrhea was present in only nine. The same authors found hepatomegaly in 29 of 33 and hepatic tenderness in all. A low grade leukocytosis was usually present.[11] These nonspecific signs and symptoms led Zavola and Hamilton to state: "Whenever [a large, tender liver] is encountered one should think of hepatic amebiasis in the differential diagnosis."[6]

Rogers and Megaw differentiate two forms of nonsuppurative hepatitis: (1) Acute hepatitis is characterized by longstanding, high intermittent fever

and liver tenderness; (2) chronic hepatitis is characterized by mild fever and leukocytosis and is often diagnosed only by therapeutic trial on emetine.[50]

In addition to those mentioned above, three others in our series of patients with symptomatic intestinal amebiasis were found on physical examination to have low grade fever and enlarged, tender livers. Two of these responded to chloroquine, and a third did not respond clinically to chloroquine but did to emetine. In each instance the ameba complement fixation test was positive prior to therapy and became negative within a few weeks after therapy had been completed. However, we have not found the ameba complement fixation test entirely reliable, even in the diagnosis of hepatic amebiasis, and we do not hesitate to make the diagnosis even in the presence of a negative test if other factors favor the diagnosis (see case 8 above).

We observed no case of amebic hepatic abscess among our patients. In a collected series of 5,211 fatal cases Ochsner and DeBakey found 36 per cent had hepatic abscess (variation in reported series was 7.6 to 84.4 per cent). The clinical incidence among 1,333 cases at Charity Hospital in New Orleans was 17 per cent of symptomatic cases requiring hospitalization.[46] Tao in Peiping, however, reports an incidence of less than 2 per cent of clinical cases.[46] Amebic hepatic abscess is rare but not unheard-of in children, and has even occurred in infants. The age range in Ochsner and DeBakey's series was six to 70.[46]

Differentiation cannot always be made with certainty between amebic hepatitis and amebic liver abscess. Zavola states: "Abscess may be suspected when there is great enlargement of the liver, marked elevation of the diaphragm, high intermittent fever, and severe systemic reaction." [6] Ochsner and DeBakey depend mostly on roentgen means, listing their criteria as elevation and fixation of the diaphragm. If the diaphragm bulges in the AP or lateral view they consider it almost pathognomonic.[46] Munk lists essentially the same criteria and groups his cases as follows: Group I: Clinical and/or radiologic enlargement of the liver without diaphragmatic signs (enlargement is not subdiaphragmatic but proceeds downward); Group II: Elevation of the right hemidiaphragm due to local or generalized enlargement of the liver, with or without restricted motion of the diaphragm and/or change in the right lower lung field; Group III: Same as Group II, but with bulging of the hemidiaphragm. Demonstration of an abscess cavity by the injection of air may be listed as a radiologic sign but is to be avoided because of the danger of rupture of the abscess into the peritoneum.[51]

A new series of symptoms and of physical and radiologic signs is produced when an amebic hepatic abscess involves the lungs and pleura. Ochsner and DeBakey found pleuropulmonary complications in 15 per cent of their patients. This complication almost always occurs by direct extension through the diaphragm and is much more rarely blood-borne. The first manifestations are likely to be right shoulder pain followed by the ex-

pectoration of chocolate colored pus. Radiologic signs are those of consolidation and effusion at the right base.[52, 46] The contents may be evacuated through a bronchopleural fistula (these patients have the best prognosis), or a chocolate sauce empyema may be produced.[53] Other complications include secondary infection of the abscess, and rupture into hollow viscera or into the peritoneum or through the skin. Secondary infection of hepatic abscesses occurs in about 15 per cent, the other complications mentioned in less than 5 per cent. Rupture into the peritoneal cavity may produce a sudden shocklike state and early death. Rupture onto the skin is likely to produce a chronically draining sinus with amebic granuloma of the skin.

Brain abscess, occurring by the hematogenous route, is so rare as barely to require mention. Manson, Bahr, Payne and others have commented on the frequency of duodenal ulcer in amebiasis. Weselmann recovered trophozoites from the duodenum in 1942.[61] We have seen the coincidence of amebic colitis and duodenal ulcer in only one patient.

Sigmoidoscopic Picture

We believe the laboratory diagnosis of amebiasis will not be made in the majority of nondysenteric patients without proctoscopic examination with direct smear of the mucosal aspirate. We have found this to be true even though we examined purged stools immediately after passage by both the direct and the zinc flotation technics. For the same reason we do not believe criteria of cure have been met until several proctoscopic examinations have been negative. The impracticality of this in civilian practice should not blind us to the fact that the ideal has not been attained. Even with proctoscopy and examination of the mucosal aspirate, we have observed patients who were apparently cured symptomatically and by laboratory findings who later relapsed with re-appearance of the parasite in the mucosal aspirate. Our feeling about the superiority of sigmoidoscopy to stool examination is shared to a greater or less degree by others.[2, 29, 55] Anderson et al. state: "The most helpful aid in diagnosis was proctoscopic examination. In 26 individuals examined, all but five showed evidence of damage to the rectosigmoid area. In the majority, ulceration was present with bleeding and hyperemia, as well as [granularity of the bowel] in longstanding cases." [2]

We have learned to expect the presence of *E. histolytica* in the aspirate whenever, on protoscopic examination, we found copious quantities of clear or greenish gray, opalescent mucus, regardless of the condition of the rectosigmoidal mucous membrane. This was our most constant finding in infected cases and was far more frequent than ulceration in our presumably early cases. Our findings are listed in table 5.

Chang reports that in 45 cases of active amebic dysentery, 50 per cent could not be diagnosed by stool examination alone but were subsequently diagnosed by sigmoidoscopy.[29] Payne estimates that 80 per cent of all cases can be diagnosed immediately by stool examination combined with sig-

moidoscopy.[8] On the other hand, D'Antoni prefers to make the diagnosis on stool examination with specimens obtained by purging and by enema. If this method is to be depended on, the need for purgation and the repeated examination of fresh stools have been emphasized by many authors. D'Antoni found that a single stool obtained by purgation detected 75 per cent of cases found on examination of six normally passed stools.[39] Lane states: "However careful an examination of one [stool] specimen is made it will show only a third of the number of positives that will eventually be found if 10 specimens are examined." [15] The common procedure of sending one or two casually passed specimens to the laboratory to be examined at leisure to "rule out" amebiasis may make the chart look more complete but

TABLE V

Out of 50 Cases:	
Mucosa normal	34 patients
Hyperemia	15 patients
Diffuse	14
Splotchy	1
Ulcers	5 patients
Mucus (clear, viscid)	Excessive in 23 patients
2 plus	9
3 plus	11
4 plus	3

is of no value in the patient's work-up. In connection with Lane's findings, quoted above, we believe a single sigmoidoscopic examination to be more productive, less laborious and less expensive and uncomfortable to the patient than the examination of 10 purged stools. However, we have on occasion found (presumably cecal) amebiasis after purging which was not found on repeated sigmoidoscopies. The two methods complement each other, and the only difference of opinion concerns which method should be the primary one.

OTHER LABORATORY FINDINGS

It has already been made apparent that the diagnosis of hepatic amebiasis is often difficult. The blood complement fixation test has been recommended in confirmation of the diagnosis, but opinions regarding its reliability vary widely, from Ochsner and DeBakey's statement that the test is highly specific for amebiasis, and particularly for amebic hepatic abscess,[46] to Lane's statement that "[the complement fixation test] is more reliable in hepatic than in intestinal cases but the percentage is not high and false positives may occur." [15] Hussey and Brown obtained the following figures:

116 patients with no evidence of amebiasis	4.3% positive
124 patients with intestinal amebiasis	3.4% positive
12 patients with proved hepatic amebiasis	83.0% positive
5 patients with probable hepatic amebiasis	80.0% positive

Variable results are attributed to the difficulty of preparing a satisfactory antigen,[15, 46] to the variation of tissue response to *E. histolytica* [55] and to

failure to use a polyvalent antigen to compensate for strain differences in *E. histolytica*.[21] Craig reports that the complement fixation test becomes negative in two to four weeks after the elimination of *E. histolytica*, and that the persistence of a positive test speaks for continued presence of the parasite.[55] The presence of *E. histolytica* in the stool is not essential for the diagnosis of hepatic amebiasis. Collected series have shown that the stool is positive in 4 to 70 per cent of such patients. These figures probably represent variations in the technic of searching for the ameba, rather than variations of such magnitude in the nature of the disease, for which there would seem to be no explanation. Leukocytosis may or may not be present[46, 45, 11]; it is not likely to be extreme. These signs, when present, in addition to the radiologic signs already discussed, must constitute the laboratory support of a diagnosis of amebic hepatitis or abscess or both.

Therapy and Response to Therapy

The literature on the therapy of amebiasis has become ever larger as new agents have been discovered, enthusiastically received, found wanting, and supplanted by new agents which, by and large, have met a similar fate. Out of all the contradictory literature certain basic principles have been emphasized:

1. "All too often the reports on the value of new amebacidal agents take no account of the enormous clinical range of the disease."[28]

2. "Clearance of ameba and ulcers at the end of a short course of treatment is very different from permanent clearance and cure."[28]

3. "[Because of burrowing and stricture formation] the longer the infection has lasted, especially if dysenteric symptoms have occurred, the more difficult is the cure."[5]

To these statements we would like to add from our own experience that (4) it is no more possible to state that the *E. histolytica* has been eradicated from the tissues of the host than it is to state that the tubercle bacillus has been eradicated from the tuberculous patient, no matter how careful the search for residual infestation. In addition to our own experience with "recurrence" (presumably incomplete cure), we have had several patients come to us with active amebiasis who had been told they were "cured" following various types of amebacidal therapy elsewhere. We are willing to say of our therapeutic successes only that they are "apparently" cured.

It is generally accepted that intestinal and extraintestinal amebacides must be different in their absorbability and distribution, that intestinal amebacides must be poorly absorbed and cannot be effective against systemic amebiasis. Dennis summarizes the qualities desired in an amebacide as follows:

1. It should be an active amebacide in the form administered, or it should be changed in vivo into an active amebacide.

2. It should be sufficiently more toxic for the ameba than for the host, i.e., should have a sufficient margin of safety.

3. The distribution of the drug should be highest at the site of infection.

4. It should remain at a therapeutic level at the infected site for a sufficient period of time.

Various older amebacidal drugs have been summarized elsewhere, particularly by Most.[1] It is not our purpose to review the literature concerning the drugs with which we have had little personal experience. Most has summarized this literature in his review, and reference might also be made to Wilmot and Armstrong's experience in the treatment of amebic dysentery which is summarized in table 6.

TABLE VI

Drug	Per Cent Success	Per Cent Probable Failure	Per Cent Failure
Emetine (gr. i I.M. daily ×15)	50	22	28
Diodoquin	58	18	24
Emetine bismuth iodide orally			
Whole	40	13	47
Crushed	56	24	20
Carbarsone	46	8	46
Yatren (chiniofon)	69	6	25
Milibis (Wia)	24	14	62

Wilmot and Armstrong defined the results of their treatment as follows: (1) Success: Symptom free. All ulcers healed. No amebae demonstrable. (2) Probable failure: Usually symptom free. One or more ulcers open but *E. histolytica* not demonstrable. (3) Failure: Ameba and ulcers demonstrated following therapy.[38]

For some years it has been customary to combine a systemic, well absorbed amebacide (emetine or, more recently, chloroquine) with a poorly absorbed "intestinal" amebacide (Diodoquin, carbarsone, etc.). The results were better than with a single drug but still left much to be desired. More recently, enthusiastic reports have appeared concerning the use of antibiotics. Because of this literature, our chief therapeutic experience has been confined to these drugs, and it is on them that we wish to report.

In vitro methods of drug testing require active proliferation of bacteria to support the growth of *E. histolytica*.[15, 22] Bradin and Hansen demonstrated that higher concentrations of antibiotics were needed to kill *E. histolytica* in tubes from which oxygen had been excluded. They concluded that bacteria potentiate the growth of amebae by maintaining a low oxidation-reduction potential, and showed in vitro by pH changes that amebic death was correlated in the course of in vitro antibiotic activity with a shift to a more positive potential. This shift did not characterize the action of previously known amebacides.[25]

Most et al. investigated the therapeutic effects of three antibiotics by mass treatment of patients in a mental institution. The patients were

divided into four groups isolated from each other in different infirmaries. By random sampling, the incidence of infection in the infirmaries was found to vary from 45 to 69 per cent. All patients (infected or not) in a given infirmary were given the same therapy. Criterion of cure was the examination of four stools by the zinc flotation technic. The results are shown in (table 7):

The experience of other authors in the use of various antibiotics is reported as follows:

Calero treated 44 cases of amebiasis, including 19 carriers and 25 symptomatic patients, of whom seven had hepatitis and one had an amebic liver abscess. He used aureomycin alone in a dosage of 30 mg./Kg./day, and the maximal total dose for any one patient was 15 gm. Of the 44 patients,

TABLE VII

Terramycin:	100% cure of 10 patients. 100% remained cured for 6 months. Incidence of disease in this infirmary (random sampling) fell from 49% to 1%.
Aureomycin:	100% cure of 18 patients. 60% remained cured after 6 months.
Bacitracin:	59% cure of 23 patients. 28% remained cured after 6 months.
Control (No Therapy):	3% of 28 patients cured.

six had negative stools during the first four post-treatment weeks, but six months later they had positive stools without symptoms. The remainder (including those with amebiasis of the liver) are stated to have become and remained negative and asymptomatic during a six month follow-up period. Calero states: "Aureomycin taken alone . . . must be considered as one of the most effective treatments of amebiasis." He reports a cure rate of 86 per cent.[29]

Most and van Assendelft state: "Clinically, active amebic colitis may be terminated by the oral administration of 80,000 units of bacitracin or 2.0 grams of aureomycin daily for 10 days. Definite cures . . . are obtained in 65 per cent and 90 per cent, respectively. The difference between these percentages and 100 per cent represents parasitic relapse . . . [but] may not be associated with evident clinical disease." [28] Hughes treated 38 patients resistant to iodoquinolines and emetine with 7 gm. of aureomycin over a four to seven day period. He reports a cure rate of 71 per cent including one patient with hepatitis who recovered. Many not parasitologically cured had symptomatic relief. His criteria of cure were absence of symptoms plus five negative purged stools within two weeks of the completion of therapy.[37] Hall reports eight out of 10 patients cured of chronic amebic dysentery, six out of six cyst passers cured, and one out of four patients with hepatitis cured after aureomycin therapy. He recommends emetine or chloroquine as combined therapy in those patients with hepatic involvement.[13] In 30 symptomatic patients treated with aureomycin, Hoekenga in Honduras

found parasitologic failure in 3 per cent two days post-therapy, but 47 per cent were positive one month later. The author notes, however, that in a highly endemic area a high incidence of re-infection was to be expected. On carbarsone plus sulfadiazine in 40 similar patients, the same author obtained almost exactly the same rate of cure at the end of one month. His criteria for cure included absence of symptoms and six negative purged stools.[14]

On the other hand, Anderson and Anderson, in experimental amebiasis in monkeys, found that the animals were free of amebiasis only temporarily with doses of aureomycin much higher than any ever given to man.[26]

Our experiences with both aureomycin and terramycin do not bear out the optimistic reports of other authors. They are shown in table 8.

TABLE VIII

Number of Patients	Remained Positive After First Course	Remained Positive After Second Course
Terramycin		
27	17 (63%)	13 (48%)
Aureomycin		
13	5 (38%)	5 (38%)

Remarks on table:

1. Of the 13 failures with terramycin, eight were given terramycin combined with emetine (7 gr. intramuscularly in seven days). Four became negative. In cases resistant to terramycin combined with chloroquine, terramycin plus emetine might be worth trying.

2. Of the five failures with aureomycin, one received emetine, aureomycin and carbarsone in a third attempt at cure but remained positive. Two received a third course of aureomycin orally combined with aureomycin retention enemas, in an attempt to bring the drug into contact with the involved portions of bowel. One of these two patients became negative. One terramycin-resistant patient received terramycin simultaneously orally and by retention enema and became negative. At the suggestion of one of us (E. J. S.), we have recently begun giving Amphogel with each dose of terramycin to delay absorption of the terramycin. We have not done this long enough to make feasible a tabulation of results, but we have the impression that the results are somewhat better.

3. Our rate of cure of 52 per cent with terramycin and chloroquine is not a significant improvement over the reported cure rate of Wilmot and Armstrong, who used conventional amebacides. It would certainly seem to refute the claims of Most and van Assendelft, who reported a 100 per cent cure rate on shorter courses of therapy than we employed, as well as the claims of Hughes and of Hall, referred to above. In so small a series, the cure rate with aureomycin is not significantly better than that obtained with terramycin.

The accompanying photomicrographs of persistent *E. histolytica* trophozoites and cysts following therapy are offered as proof of our failure to

obtain cure. They are iron hematoxylin stains of material obtained at proctoscopy (figures 5, 6).

We have already stated that because of the imperfection of our diagnostic methods, even these results may later have to be revised downward.

It must be pointed out that, to achieve therapeutic results, the toxic effects of these antibiotics are deliberately sought. To obtain amebacidal effect, it

FIG. 5. This patient received two courses of terramycin (each 20 gm. in 10 days). Mucosal aspirate shows two trophozoites of *E. histolytica* (iron-hematoxylin stain).

is necessary to bring about a change in the bacterial flora of the bowel and thereby court overgrowth of other pathogenic organisms, particularly monilia and hemolytic *Staphylococcus aureus*, with resulting colitis against which antibiotic therapy has little or no effect and which may persist for long periods of time. The hazards are emphasized in an excellent article by Jackson et al., who treated 91 patients with terramycin for atypical pneumonia. Seven deaths occurred in this series, all in debilitated patients, and in each instance superinfection with terramycin-resistant organisms was either a direct or a contributing factor. Five of the seven had hemolytic *S. aureus* in the stools or sputum or blood. One had monilia in the stools and proteus in the urine.[57]

We were moved by this article to culture the stools of five of our patients in whom prolonged, persistent diarrhea developed in the course of terramycin therapy. Three of these grew hemolytic S. *aureus* which was resistant

to terramycin in vitro. The proctoscopic picture in these patients was distinctly worse than it had been at the start of therapy, regardless of the effect of therapy on the amebae. All recovered normal bowel function after a more or less protracted period of diarrhea. It is to be emphasized that our patients were all young and in good physical condition, and that superinfection might have been a much more serious problem in other population groups. It is to be further emphasized that the results obtained were derived from a spot check of our more severe post-treatment diarrheas, and that many other patients with less severe symptoms may also be presumed to have had superinfection.

Toxic effects of emetine were not noted in the few patients in whom we used it. There was no change in electrocardiograms taken on these patients. However, no patient in our series received more than 14 gr. of emetine.

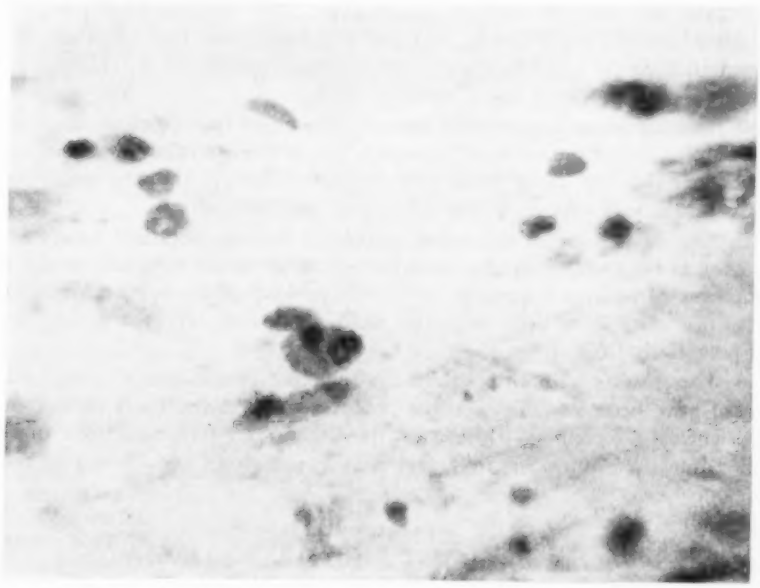


FIG. 6. This patient received two courses of terramycin similar to those received by the patient in figure 5. He also had terramycin by retention enema. A cyst of *E. histolytica* is present in the mucosal aspirate.

It is the consensus of the literature that toxicity from emetine is rare when the total dose is low.[1, 5, 35] Chloroquine, which was used routinely in all our patients for either prophylactic or therapeutic reasons, caused minor toxicity in almost all patients, manifested by nervousness and slight blurring of vision. Syncope, presumably attributable to chloroquine, occurred in three patients and one of these had convulsions. These manifestations have also been

noted in the literature.[15] We stopped chloroquine therapy only where more severe toxic manifestations were noted than the almost universal nervousness and depression.

Summary and Conclusions

1. Fifty patients with amebiasis of the colon or liver or both have been observed at an Army installation. Some but by no means all of these patients had served in the Far East. Emphasis is placed on the unusual clinical pictures that may occur and on the need for awareness of the prevalence of this disease in both civilian and military medicine. This will be pointed up by the return to civilian life of large numbers of men who have served in the Far East.

2. We feel that sigmoidoscopy, with immediate examination of specimens of mucus for *E. histolytica,* is the most practical method of diagnosis; it is easier and more productive, in our experience, than frequently repeated examinations of purged stools, and our experience and that of others have shown that single stool specimens, or repeated specimens not obtained by purging, result in a very low diagnostic yield.

3. For the reasons expressed under (*2*) we feel that sigmoidoscopy and the examination of the mucosal aspirate is one of the essential criteria of cure. We believe that the use of lesser criteria has resulted in the overenthusiastic and contradictory reports of the efficacy of antibiotic drugs.

4. Our experience in the use of antibiotics for the intestinal form of the disease has been disappointing, both in failure to obtain cure and in the development of serious untoward effects on prolonged therapy. Our results with antibiotics have been no better than previously reported results with less potentially toxic drugs.

5. Our results with chloroquine and emetine in the hepatic form of the disease have been variable; we are not prepared, on the basis of our own experience, to recommend one over the other. Re-infection from uncontrolled intestinal amebiasis may give a false picture of the efficacy of these drugs.

Acknowledgment

The authors gratefully acknowledge the assistance of Lt. Colonel Willard Angen, Captain Herbert Virden and Miss Wilma Frazer, who gave freely of their time in helping to prepare this paper.

BIBLIOGRAPHY

1. Most, H.: Recent advances in the therapy of the more common protozoan and helminthic infections of man, Bull. New York Acad. Med. **25**: 717-740 (Nov.) 1949.
2. Anderson, H. H., Johnstone, H. G., Packer, H., Young, J. D., Callison, M. K., Hambly, A. S., Jr., Anderson, J. Van D., and Reed, R. K.: Incidence and control of amebiasis and other protozoan infections in a Memphis hospital, Am. J. Trop. Med. **28**: 373-382, 1948.
3. Callender, G. R.: Dysenteries and diarrheas—their importance in military service, War Med. **4**: 459-464 (Nov.) 1943.

4. McVay, L. V., Laird, R. L., and Sprunt, D. H.: A preliminary report of the successful treatment of amebiasis with aureomycin, Science **109**: 590, 1949.
5. Hargreaves, W. H.: The treatment of amebiasis with special reference to chronic amebic dysentery, Quart. J. Med. **15**: 1–21, 1946.
6. Zavola, D. C., and Hamilton, H. E.: Recognition and treatment of hepatic amebiasis, Ann. Int. Med. **36**: 110–125 (Jan.) 1952.
7. Sandler, R.: Chronic involvement of the liver in intestinal amebiasis, Am. J. Digest. Dis. **18**: 29 (Jan.) 1951.
8. Payne, A. M. M.: Amebic dysentery in Eastern India, Lancet: **1**: 206–209, 1945.
9. Palmer, R. B.: Histopathology of the liver in amebiasis, Arch. Path. **25**: 327, 1938.
10. Sodeman, W., and Lewis, B. O.: Amebic hepatitis, Am. J. Trop. Med. **25**: 35–39 (Jan.) 1945.
11. Sodeman, W., and Lewis, B. O.: Amebic hepatitis: report of 33 cases, J. A. M. A. **129**: 99–104 (Sept. 8) 1945.
12. Wright, W. H.: The public health status of amebiasis in the United States as revealed by available statistics, Am. J. Trop. Med. **30**: 123, 1950.
13. Hall, W.: Treatment of chronic human amebiasis with aureomycin, New England J. Med. **244**: 495 (Apr. 5) 1951.
14. Hoekenga, M. T.: Comparison of aureomycin and carbarsone in the treatment of intestinal amebiasis, Am. J. Trop. Med. **31**: 423, 1951.
15. Lane, R.: Treatment of hepatic amebiasis with chloroquine, J. Trop. Med. **54**: 198 (Oct.) 1951.
16. Conan, N. J., Jr.: Treatment of amebic hepatitis with chloroquine, Am. J. Med. **6**: 309, 1949.
17. Sodeman, W. A.: Clinical picture of hepatic amebiasis, Am. J. Trop. Med. **30**: 141, 1950.
18. Hussey, K. L., and Brown, W. H.: The complement fixation test for hepatic amebiasis, Am. J. Trop. Med. **30**: 147, 1950.
19. Tobie, J. E., Most, H., Reardon, L. V., and Bozicevich, J.: Laboratory results of the efficacy of terramycin, aureomycin, and bacitracin in the treatment of asymptomatic amebiasis, Am. J. Trop. Med. **31**: 414, 1951.
20. Calero, C.: Aureomycin in the treatment of intestinal amebiasis, Am. J. Trop. Med. **31**: 566 (Sept.) 1951.
21. Bozicevich, J.: Discussion of,[18] Am. J. Trop. Med. **30**: 156, 1950.
22. Spingar, C. L., and Edelman, M. H.: The effect of aureomycin hydrochloride on the growth of *E. histolytica* in vitro, Am. J. Trop. Med. **31**: 206 (Mar.) 1951.
23. Dennis, E. W.: Discussion of chemotherapy of amebiasis in amebiasis panel, Am. J. Trop. Med. **30**: 159, 1950.
24. Bradin, J. L., and Hansen, E. L.: Indirect in vitro action of antibiotics: comparison with accepted amebacides, Am. J. Trop. Med. **30**: 27–41, 1950.
25. Ibid., pp. 193–201.
26. Anderson, H. H., and Anderson, J.: Amebiasis panel; amebiasis in macaques, Am. J. Trop. Med. **30**: 193–201, 1950.
27. Nushan, H., and Miller, B.: Ameboma of the transverse colon, Ann. Int. Med. **37**: 372, 1952.
28. Most, H., and van Assendelft, F.: Terramycin in the treatment of amebiasis; laboratory and clinical observations, Ann. New York Acad. Sc. **53**: 427, 1950.
29. Chang, H. C., Chen, K. C., and Chou, S. K.: Further observations on the diagnosis of amebic dysentery, Chinese M. J. **50**: 17–26 (Jan.) 1936.
30. Ochsner, A., and DeBakey, M.: Surgical amebiasis, The New International Clinics: Vol. I, New Series Five, 68–99 (Mar.) 1942.
31. Hines, L. E.: A form of polypoid colitis as a late stage of amebic dysentery, J. A. M. A. **81**: 12, 1923.
32. Anderson, H. H.: Amebiasis and pseudopolyposis of the colon, J. A. M. A. **107**: 2121, 1936.

33. Sodeman, W. A., and Beaver, P. C.: A study of the therapeutic effects of some amebacidal drugs, Am. J. Med. **12**: 440–446, 1952.
34. Conan, N. J., Jr.: The treatment of amebic hepatitis with chloroquine, Bull. New York Acad. Med. **24**: 545–546, 1948.
35. Palmer, R. B.: Military amebiasis, Am. J. Trop. Med. **26**: 543, 1946.
36. Conan, N. J., Jr.: Chloroquine in amebiasis, Am. J. Trop. Med. **28**: 107–110, 1948.
37. Hughes, J. D.: Treatment of amebiasis with aureomycin; report of 38 cases, J. A. M. A. **142**: 1052–1054, 1950.
38. Wilmot, A. J., and Armstrong, T. G.: Treatment of amebic dysentery in Bantu African, Tr. Roy. Soc. Trop. Med. and Hyg. **42**: 597–604 (May) 1949.
39. D'Antoni, J. S.: Amebiasis: recent concepts of its prevalence, symptomatology, diagnosis and treatment, The New International Clinics: Vol. I, New Series Five, p. 100 (Mar.) 1942.
40. Read, W. A., and Hushan, H.: Amebic granuloma simulating carcinoma, Gastroenterology **15**: 771–779 (Aug.) 1950.
41. Berberian, D. A., Dennis, E. W., and Pipkin, C. A.: The effectiveness of Milibis in amebiasis, Am. J. Trop. Med. **30**: 613, 1950.
42. Ibid., pp. 193–201, 1950.
43. Seneca, H., and Henderson, E.: Combined antiamebic and antibacterial treatment of intestinal amebiasis, Am. Pract. and Digest Treat. **1**: 960 (Sept.) 1950.
44. Radke, R.: Incidence of amebiasis in Korean veterans, U. S. Armed Forces M. J. **3**: 323 (Feb.) 1952.
45. Klatskin, G.: Amebiasis of the liver; classification, diagnosis, and treatment, Ann. Int. Med. **25**: 601, 1946.
46. Ochsner, A., and DeBakey, M.: Amebic hepatitis and hepatic abscess, Surgery **13**: 460, 1943.
47. Radke, R.: Amebiasis with hepatic abscess and pleuropulmonary involvement, U. S. Armed Forces M. J. **2**: 437–444 (March) 1951.
48. McVay, L. V., Laird, R. L., and Sprunt, D. H.: The treatment of amebiasis with aureomycin, South. M. J. **43**: 308–313, 1950.
49. Meleney, J. E.: The pathology of amebiasis, J. A. M. A. **103**: 1213, 1934.
50. Rogers, L.: Amebic liver abscess, Lancet **1**: 463, 1922.
51. Munk, J.: X-ray appearance in amebic hepatitis, Brit. J. Radiol. **17**: 48, 1944.
52. Pancoast, H. K.: The roentgenologic diagnosis of liver abscess with or without subdiaphragmatic abscess, Am. J. Roentgenol. **16**: 303, 1926.
53. Ochsner, A., and DeBakey, M.: Amebic hepatitis and hepatic abscess, Surgery **13**: 612, 1943.
54. Sodeman, W. A., and Lewis, B. O.: Amebic hepatitis, Am. J. Trop. Med. **25**: 35, 1945.
55. Craig, C. F.: Amebiasis and the complement fixation test, U. S. Armed Forces M. J. **1**: 1337–1342, 1950.
56. Hussey, K. L., and Brown, H. W.: The complement fixation test for hepatic amebiasis, Am. J. Trop. Med. **30**: 147–157, 1950.
57. Jackson, G. G., Haight, T. H., Kass, E. H., Womack, C. R., Gocke, T. M., and Finland, M.: Terramycin therapy of pneumonia: clinical and bacteriologic studies in 91 cases, Ann. Int. Med. **35**: 1175–1202 (Dec.) 1951.
58. Faust, E. L.: The prevalence of amebiasis in the Western Hemisphere, Am. J. Trop. Med. **22**: 93, 1942.
59. Jacobs, L., Wallace, F. G., and Diamond, L. S.: Survey of intestinal parasites in soldiers being separated from service, Bull. U. S. Army M. Dept. **6**: 259–262 (Sept.) 1946.
60. Rogers, L., and Megaw, J. W. D.: Tropical medicine, 4th Ed., J. & A. Churchill, Ltd., London, 1942.
61. Weselmann, H.: Vorkommen von Entamoeba histolytica im Duodenum, Deutsche tropenmed. Ztschr. **46**: 457, 1942.

TESTING FOR ANTIBIOTIC SENSITIVITY IN A GENERAL HOSPITAL *

By A. J. Weil, M.D., and L. Harris, M.D., F.A.C.P., *New York, N. Y.*

Experimental data and clinical experience have produced rules which direct the choice of antibiotic agents in daily practice. Most of the work on which these rules are based was obtained from "virgin" material, virgin in the sense that the microörganisms studied had not previously been exposed to antibiotics. The wide use of these agents has created a different situation. An organism that was originally susceptible may be replaced by resistant mutants in the individual case and eventually throughout its habitat. Perhaps the best known example of this change is that of the susceptibility of *Staphylococcus aureus* to penicillin, which has declined from the original 100 per cent to about 50 to 60 per cent of isolations in this country [1] as well as abroad.[2] Epidemic spread of resistant strains has repeatedly been reported.[1b] Moreover, there is a definite tendency under the influence of antibiotic therapy to replace a susceptible microbial flora by a different and resistant one.[3] The question arises whether, at the present juncture, the established rules of therapeutic procedure can be relied upon to the point where it would be safe to dispense with the checks of the individual case afforded by laboratory procedures. A review of the presently prevailing situation appears timely.

The data collected at this hospital may serve as a contribution to an appraisal of our position, the more so as they may be considered representative of a very common situation, namely, that prevailing in a general hospital. Our institution, with about 400 beds (including bassinets), has all the usual medical and surgical services but does not admit contagious diseases and has no tuberculosis wards. Most of the patients are admitted by the physicians of our visiting staff for reasons of medical necessity and not for the social ones, such as lack of care at home, which motivate many admissions to institutions dedicated primarily to the destitute. As far as cases treated with antibiotics are concerned,† this circumstance is likely to exercise a definite selective influence. On the one hand, conditions which yield promptly to routine antibiotic treatment are not frequently hospitalized. (In this respect, it is probably characteristic that very few pneumococci were isolated in this hospital during the period covered by this report, and that in no case of pneumococcal etiology were tests for antibiotic sensitivity re-

* Received for publication November 7, 1952.

From the Department of Bacteriology, The Bronx Hospital, New York, N. Y.

† In about 75 per cent of the cases reviewed here there was a record of treatment with antibiotics previous to bacteriologic examination. In about 40 per cent of these penicillin had been used; in 30 per cent, penicillin plus one or more of the other antibiotics; in 30 per cent, one or more antibiotics other than penicillin.

quested.) On the other hand, failure of home treatment with antibiotics will be a relatively frequent cause for hospital admission. Moreover, as bacteriologic examination is not compulsory, it will sometimes be requested only when previous therapy has not shown the expected results, or when complications have occurred. These circumstances are likely to be conducive to a statistical bias in favor of uncommon etiologic agents, or of microorganisms with unexpected behavior toward antibiotics. It was the question of the incidence of such deviating behavior which motivated this review of our experience.

Material and Methods

A routine for testing for susceptibility to antibiotics was established in this hospital in December, 1950, covering in each case penicillin, aureomycin, chloramphenicol, terramycin, streptomycin, dihydrostreptomycin and bacitracin.

Tests were made with the disk method, using the divided plate of Felsen, as recently described.[4]

In the great majority of cases, the disks manufactured by Difco Laboratories (Detroit) were used. We feel that the use of disks in three concentrations is helpful both as an aid in estimating the degree of sensitivity and as a control. Only pure cultures were tested.

A word of comment concerning the validity of this method may be in order, as a recent discussion of this subject [5] culminated in a statement full of misapprehensions which was widely distributed by one of the manufacturers of antibiotics. The disk method [4, 6] as widely practiced with commercially available disks or tablets is not a quantitative method. Under carefully controlled conditions the disk method is as amenable to quantitative treatment [6a] as any other method of antibiotic assay. However, too many variables enter into the procedure as routinely practiced to permit reliable quantitative estimates. By the same token, other methods of antibiotic assay are also subject to large errors unless scrupulously exact technics and statistical control are practicable. But if used with due consideration of the factors involved, the disk method permits a reasonably accurate distinction between high or low in vitro susceptibility or the absence of inhibition. All investigators of this technic agree about this.[6a, b, c, d] Such an appraisal is, in fact, all that is needed for practical clinical purposes since, besides the question of the correlation between in vitro and in vivo effect, the variables introduced by dosage and other factors are much too great to permit utilization of more quantitative data (except, of course, for special investigational purposes).

Besides the advantages of expediency and speed, the method often permits the observation of resistant mutants which enables the laboratory to give forewarning of an impending change in the usefulness of an antibiotic (figure

1). (Where such mutants were seen, the result was counted in the following as evidence of resistance.)

Altogether, 330 cultures were examined during the period from December 1, 1950, to April 1, 1952. For the purposes of this survey, the following major groupings were distinguished:

1. Streptococci. Of the 88 strains, 10 were beta hemolytic (*Streptococcus pyogenes*), 37 alpha hemolytic, 10 nonhemolytic; 27 were classified

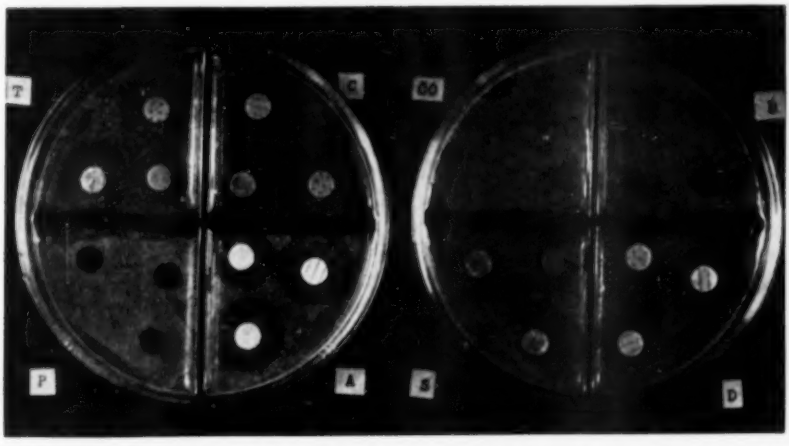


FIG. 1. Demonstration of mutants resistant to aureomycin and terramycin by the disk method. *E. coli* was obtained as the predominant organism from the throat of a patient who had taken four troches of aureomycin in a 36 hour period.

P—penicillin
A—aureomycin
C—chloramphenicol
T—terramycin
S—streptomycin
D—dihydrostreptomycin
B—bacitracin
CO—control

Inhibition of growth surrounding chloramphenicol disk; zones of inhibition around the disks with aureomycin and terramycin speckled with colonies of resistant mutants.

according to their cultural properties, as *S. fecalis*, and four were strongly proteolytic. Analysis showed that little would be gained by a separate accounting for these subdivisions, because no essential differences in their reactivity to antibiotics were seen, except that all but one strain of *S. pyogenes* were found inhibited by penicillin.

2. Staphylococci (*Micrococcus pyogenes*). Among 86 strains, 71 were of the golden and 15 of the white variety, but each fermented mannitol and produced coagulase.

3. The "colon group," comprising 59 strains. Of these, 46 would properly be classified as escherichia and 13 as aerobacter. Again, analysis suggested the treatment of these species as one group, as no significant differences in susceptibility to antibiotics came to the fore.

TABLE I

In Vitro Sensitivity (Organisms of High Incidence)

Organism	Number Tested	Per Cent Sensitive to					
		Penicillin	Aureomycin	Chloramphenicol	Terramycin	Streptomycins	Bacitracin
Streptococcus	88	77	64	92	64	20	80
Staphylococcus	86	57	65	93	69	40	87
Colon Group	59	0	46	83	70	36	2
Proteus Group	52	4	6	60	6	21	2
Pyocyaneus	23	0	0	13	0	4	0

4. Proteus, comprising 52 strains. Variation in cultural behavior was not correlated with differences in antibiotic sensitivity.

5. *Pseudomonas aeruginosa* (*Ps. pyocyanea*), comprising 23 strains.

Several other species, of which only small numbers were encountered, are listed separately.

RESULTS

The over-all data of the five major groups are tabulated in table 1. Column 2 shows the number of strains examined, columns 3 to 8 the percentage found susceptible to the various antibiotic agents. As streptomycin and dihydrostreptomycin gave identical results, they are listed together here and in the following as "the streptomycins."

The results with the strains collected in small numbers are tabulated in table 2. The figures in columns 3 to 8 give the actual number of strains found susceptible.

COMMENT ON THE RESULTS OF TESTING

Three points stand out in the results obtained with our material:

1. The relatively low percentages of penicillin susceptibility among the gram-positive cocci. For staphylococci, this is in accordance with the find-

TABLE II

In Vitro Sensitivity (Organisms Tested in Small Numbers)

Organism	Number Tested	Sensitive to					
		Penicillin	Aureomycin	Chloramphenicol	Terramycin	Streptomycins	Bacitracin
Bethesda Group	5	0	0	2	0	0	0
Alkaligenes fecalis	3	1	2	1	3	2	1
Klebsiella pneumoniae	1	0	0	0	1	0	0
Shigella alkalescens	4	0	3	4	3	2	0
Sh. flexneri, type 6	1	0	1	1	1	0	0
Salmonella bredenay	1	0	1	1	1	1	0
Neisseria meningitidis	1	1	1	1	1	0	1
Hemophilus influenzae, type B	6	1	6	6	6	3	0

ings elsewhere at the present time, as pointed out initially. As to the streptococci, the figure is conditioned by the fact that the majority of the isolations consisted of alpha hemolytic streptococci and those of the fecalis group. The low inclination of beta hemolytic *S. pyogenes* to form penicillin-resistant mutants is suggested not only by our findings but also, by inference, by the low rate of occurrence among hospitalized patients.

2. The high over-all efficiency of chloramphenicol, in comparison with aureomycin and terramycin. Our records show that the latter two agents were used far more frequently than chloramphenicol in the period preceding bacteriologic examination. Thus, one possible explanation of our findings is that we encountered a significant number of strains that had produced resistant mutants under the influence of the treatment. An alternative though perhaps more remote possibility is that resistant strains have already become widespread among the microbial flora in this city.

As to proteus, the frequent occurrence of strains susceptible to chloramphenicol but not to others of the agents discussed here has recently been reported from two sources.[7]

3. The low over-all "score" of the streptomycins. For its explanation, considerations similar to those offered in the preceding paragraphs may apply.[2a]

The high percentage of gram-positive cocci susceptible to bacitracin is worthy of note because of its relevance to the treatment of streptococcal and staphylococcal lesions accessible to local treatment.

Clinical Correlation

A careful review of the records yielded no instance where clinical experience was in contradiction to the outcome of in vitro sensitivity tests. This is in agreement with the good correlation between the outcome of sensitivity tests with the disk method and clinical experience just reported from Detroit.[8]

As to the aid to clinical procedure provided by in vitro testing for sensitivity, incontrovertible evidence is not easily obtained. After all, a good many cases would have run a favorable course without antibiotics. And the outcome of the tests often will only confirm the correctness of the choice of treatment made by necessity before laboratory data became available. Moreover, it is impossible to say how many of the changes in therapeutic procedure ordered upon receipt of the laboratory report might have been made anyhow from purely clinical considerations.

However, in about one out of seven cases a change in antibiotic treatment was initiated when reports of the laboratory indicated that the organism isolated would not be susceptible to the currently employed drug. In many of these cases, one could not fail to be impressed by the likelihood that this change was helpful.

A few examples may be quoted in support of this impression:

A meningitis caused by *E. coli* was initially treated with aureomycin,

without striking result. Tests showed this strain resistant to aureomycin but susceptible to chloramphenicol, and a change to this drug was followed by a prompt, favorable response.

An abscess developed beneath the operation wound of an appendiceal abscess which had been treated before and after the surgical intervention with penicillin. The *Staphylococcus aureus* isolated from the cutaneous abscess proved to be resistant to penicillin but responsive to aureomycin and other agents. Progress after surgical drainage was slow until aureomycin was substituted for penicillin. Prompt recovery ensued.

From a peritonitis subsequent to a ruptured appendix, a colon strain was isolated which proved resistant to aureomycin but sensitive to chloramphenicol. Aureomycin given before the tests were completed did not visibly influence the infection. A switch to chloramphenicol was followed by rapid improvement.

Proteus was isolated from a severely infected amputation wound. The only agent to which this microörganism was susceptible was chloramphenicol. Treatment with penicillin and aureomycin had proved of no avail. A change to chloramphenicol was followed by rapid cleaning of the wound.

Significance of Etiologic Information

One interesting aspect of our data is the high incidence of uncommon bacteria, or of bacteria with unexpected antibiotic "spectra" among the type of material for which this report is representative. Thus a full third of our isolations of organisms of the colon group, of proteus and of pyocyaneus bacilli came from locations where these organisms are not commonly found, such as blood cultures, meningitis and osteomyelitis. As to positive blood cultures, only two concerned beta hemolytic streptococci and four *S. aureus,* but six concerned alpha hemolytic streptococci or *S. fecalis,* five members of the colon group, one proteus, one *B. alkaligenes,* two *H. influenzae,* type b, and one *Ps. aeruginosa.* If one subtracts from these 22 cases the eight where the clinical aspect of the disease (endocarditis or meningitis) gave some indication of the probable causative agent, 14 cases remain where the tentative diagnosis was septicemia of unknown origin. Seven of these yielded gram-negative rods. Of nine cases of meningitis, six concerned *H. influenzae,* type b, and one each *Neisseria meningitidis, E. coli* and *Staph. aureus.*

In the hospital as well as in private practice, decisions concerning initiation or change in antibiotic therapy have to be made when bacteriologic data are not (or not yet) available. From our experience it would appear that history of previous treatment with antibiotics and any circumstance suggesting the presence of uncommon or resistant organisms should influence such decisions. In case of doubt, our data would indicate that the statistical likelihood of finding a "fitting" antibiotic would, under the conditions outlined, favor the choice of chloramphenicol, followed by terramycin and aureo-

mycin and, in third line, penicillin or the streptomycins.* For the treatment of infections caused by gram-positive cocci and accessible to local therapy, bacitracin merits consideration for two reasons: Exceptions from the rule of the susceptibility of these organisms to this agent are rare. And its use will prevent possible allergic sensitization to other agents which may preclude their employment at a time of urgent need.

If it is true that resistant mutants of common pathogenic microörganisms are becoming more prevalent, and if previous antibiotic therapy frequently opens the door to microbial invaders of a kind rarely encountered in the past, the need to be on the alert against surprises is obvious. The best insurance against disappointments is to investigate the nature of the infecting agent in every case where antibiotic treatment is considered, and to do so in time and, if the situation warrants, repeatedly. The importance of proper bacteriologic control has increased rather than decreased. Mutual understanding and coöperation between the clinical and the bacteriologic departments and high standards of laboratory performance are more important than ever.

In view of the need for early information, bacteriologic findings should be reported at three levels:

1. Gram stain of the direct smear. This simple and too often neglected method makes available within minutes valuable information concerning the kind and abundance of microörganisms present.
2. Culture and identification by biologic and immunologic methods of the organisms involved.
3. Tests for antibiotic sensitivity to the fullest extent that available facilities permit.

Summary

The results are reported of 330 consecutive in vitro tests for antibiotic susceptibility of microörganisms collected in a general hospital. Numerous instances of unexpected resistance were noted. Taken in conjunction with the high incidence of unusual microörganisms isolated from blood cultures and local sites of infection noted during this investigation, this indicates the need to be on the alert against happenings of this kind under conditions where cases previously subjected to antibiotic treatment are frequently encountered; and it emphasizes the need for individual bacteriologic investigation and testing for antibiotic sensitivity.

Addendum

Since this paper was submitted for publication, a report by Y. Chabbert, of the Institut Pasteur in Paris (Ann. Inst. Pasteur **80**: 627, 1951), has come to our attention. Tests for sensitivity to penicillin, streptomycin, aureomycin, chloramphenicol and terramycin with 700 strains collected from hospital material are recorded which, in their essential results, parallel

* Needless to say, this choice may have to be tempered by clinical considerations, particularly those concerning allergic reactivity and the other undesirable side effects of these agents.

our experience, particularly concerning the wide variation in sensitivity not only to penicillin but also to other antibiotics, and the increased finding of resistant strains among gram-positive cocci and enterobacteriaceae from hospital material observed during recent years.

BIBLIOGRAPHY

1. (a) Finland, M., Frank, P. F., and Wilcox, C.: In vitro susceptibility of pathogenic staphylococci to 7 antibiotics, Am. J. Clin. Path. **20**: 325–334 (April) 1950.
   (b) Felsen, J., Lapin, J., Wolarsky, W., Weil, A. J., and Fox, I.: Staphylococcic infections in hospital nurseries and pediatric wards, Am. J. Dis. Child. **81**: 534–540 (April) 1951.
2. (a) Rountree, P. M., Barbour, R. G. H., and Thomson, E. F.: Incidence of penicillin-resistant and streptomycin-resistant staphylococci in a hospital, Lancet **1**: 435–436 (Feb. 24) 1951.
   (b) North, E. A., and Christie, R.: Acquired resistance of staphylococci to action of penicillin, M. J. Australia **1**: 176–179 (Feb. 9) 1946.
3. Jackson, G. G., Haight, T. H., Kass, E. H., Womack, C. R., Gocke, T. M., and Finland, M.: Terramycin therapy of pneumonia: clinical and bacteriological studies in 91 cases, Ann. Int. Med. **35**: 1175–1203 (Dec.) 1951.
4. Felsen, J., and Weil, A. J.: The divided culture plate. Its use in testing for sensitivity to antibiotics, Arch. Int. Med. **88**: 406–408 (Sept.) 1951.
5. Editorial: Laboratory control of antibiotic therapy, J. A. M. A. **147**: 1360–1361 (Dec. 1) 1951.
6. (a) Sherwood, M. B., De Falco, E. A., and De Beer, E. J.: A rapid, quantitative method for the determination of penicillin, Science **99**: 247–248 (March 24) 1944.
   (b) Erlanson, P.: Determination of the sensitivity in vitro of bacteria to chemotherapeutic agents, Acta path. et microbiol. Scandinav., Supp. **85**: 1–162, 1951.
   (c) Spaulding, E. H., and Anderson, T. G.: Selection of antimicrobial agents by laboratory means, J. A. M. A. **147**: 1336–1340 (Dec. 1) 1951.
   (d) Patrick, W. C., Craig, G. H., and Bachman, M. C.: Diameter of inhibiting zones correlated with tube sensitivities using six antibiotics, Antibiotics and Chemotherapy **1**: 133–137 (May) 1951.
7. (a) Rhoads, P. S., Billings, C. E., and O'Conor, V. J.: Antibacterial management of urinary infections, J. A. M. A. **148**: 165–170 (Jan. 11) 1952.
   (b) Ronsmeier, J. C., Brown, H. E., and Davis, N.: Comparison of in vitro sensitivity of freshly isolated pathogenic bacteria to terramycin and other antibiotics (aureomycin, chloramphenicol, penicillin and streptomycin), J. Lab. and Clin. Med. **38**: 620–630 (Oct.) 1951.
8. Broom, N. H., Martineau, P. C., and Young, D. C.: A correlation of the results of disk antibiotic sensitivity tests and the clinical course of one hundred patients, Bact. Proceed. 1952, pp. 120–121 (Meeting of the Soc. of Am. Bacteriologists, Boston, April 27 to May 1, 1952).

PLASMA CELL MYELOMA *

By Gordon C. Meacham, M.D., *Cleveland, Ohio*

Introduction

Plasma cell myeloma is a well known disease often associated with obvious clinical and pathologic findings. However, in a study of 51 patients with this disease at the University Hospitals of Cleveland since 1933, it was apparent that certain aspects of the disease have not been sufficiently recognized. In particular, the type of anemia, the character of radiologic changes in the bones, sternal marrow findings and certain metabolic disturbances, if recognized as being part of the disease, may permit an earlier diagnosis than would otherwise be the case. Abnormal hematologic, orthopedic, metabolic and renal manifestations may occur during the course of this disease, and symptoms referable to any one or to a combination of the above may be the first noted by the patient.

Definition: Plasma cell myeloma has been defined [1] as a malignant disease characterized by diffuse involvement of the osseous system, with production of bone pain and pathologic fractures, and associated with Bence-Jones proteinuria. Significant laboratory findings include anemia, abnormal roentgenologic findings in the bones, hyperglobulinemia, increased number of plasma cells in the marrow, Bence-Jones proteinuria, hypercalcemia with a normal alkaline phosphatase, small numbers of plasma cells in the peripheral blood, and excessive rouleaux formation of the erythrocytes, with a rapid erythrocyte sedimentation rate. The outcome is uniformly fatal.

Table 1

Age Incidence of 51 Patients with Plasma Cell Myeloma

Age (Years)	Number of Patients
Under 40	3
40–49	6
50–59	19
60–69	16
70–70	7
Total	51

Age and Sex Distribution: In the present series of 51 patients there were 22 females and 29 males. The age at the onset of symptoms ranged from 35 years to 75 years (table 1). Forty-two patients, or 82.3 per cent, were 50 years or older, a finding in accordance with the previous observation [2] that the great majority of cases occur in later life. The sex incidence in this series is compatible with previous observations that this disease is more prevalent in males.

* Received for publication January 9, 1953.

From the Department of Medicine, Western Reserve University School of Medicine, Cleveland, Ohio.

Anemia: This is one of the most important findings in plasma cell myeloma. It is almost invariably present and may be the only abnormal finding when the patient is first seen. In only four patients in this series was the initial erythrocyte count over 4,000,000 cells per cubic millimeter, and in no case did it exceed 4,500,000 cells per cubic millimeter (table 2).

TABLE II

Distribution of Initial Erythrocyte Counts in 51 Patients with Plasma Cell Myeloma

Initial Erythrocyte Count (cells per cu.mm.)	Number of Patients
4,000,000–4,499,000	4
3,500,000–3,999,000	10
3,000,000–3,499,000	8
2,500,000–2,999,000	11
2,000,000–2,499,000	11
1,500,000–1,999,000	7
Total	51

The anemia in plasma cell myeloma is generally considered to be normocytic in type.[1] In this series the mean corpuscular volume was determined in 29 patients, and in 22 it exceeded 95.0 cubic microns. If the statement [1] is accepted that a mean corpuscular volume exceeding 95.0 cubic microns constitutes macrocytosis, 75.9 per cent of these patients showed macrocytosis on initial laboratory examinations. Six patients had normocytic anemia, whereas microcytic anemia was observed only once (table 3).

The occurrence of macrocytic anemia in plasma cell myeloma has not been emphasized adequately. In any instance of macrocytic anemia of unknown cause, plasma cell myeloma should be considered. In our own experience it has led to an erroneous tentative diagnosis of pernicious anemia, the macrocytosis being of sufficient degree and sufficiently obvious on the

TABLE III

Erythrocyte Size in 29 Patients with Plasma Cell Myeloma

Mean Corpuscular Volume (cubic microns)	Number of Patients
Over 95	22
80–95	6
Less than 80	1
Total	29

blood film to suggest that condition. Patients have been referred with a diagnosis of "pernicious anemia which does not respond to treatment," in whom a diagnosis of plasma cell myeloma was subsequently established and in whom the error in diagnosis was fostered by a failure to recognize the fact that macrocytic anemia occurs in association with plasma cell myeloma.

Radiologic Bone Findings: Roentgenologic studies of the bones, including at least the skull and either the lumbar vertebrae or the pelvis, or both, were made in 50 patients. In one case only the ribs were so examined. Definite osseous abnormalities were present in 48 instances. In 30 patients

(58.8 per cent), discrete osteolytic lesions in conjunction with diffuse osteoporosis occurred; in 10 patients (19.6 per cent), only localized, so-called "punched out" lesions were found. In seven patients (13.7 per cent), diffuse osteoporosis was the only pathologic finding radiographically. In three patients (15.8 per cent), no bone abnormalities were present. In one instance a compression fracture of the sixth thoracic vertebra was the only radiologic osseous defect.

The rounded, "punched out" osteolytic bone lesions are a well recognized finding in plasma cell myeloma, whereas diffuse osteoporosis has received insufficient emphasis. In these series diffuse osteoporosis was a common finding. In general, the osteolytic lesions and the osteoporosis occurred together. In seven cases, however, osteoporosis was the sole radiologic manifestation of the disease. One of these patients was under treatment for "senile osteoporosis" because it was not recognized that plasma cell myeloma can be associated with diffuse osteoporosis without having localized lesions. Furthermore, senile osteoporosis very rarely involves the bones of the skull, whereas the osteoporosis of plasma cell myeloma, like that of hyperparathyroidism, frequently involves this site. Any patient with diffuse osteoporosis, particularly if the bones of the cranium are involved, and unexplained anemia should be investigated for the presence of plasma cell myeloma. It should be emphasized, however, that radiologic bone surveys may be entirely normal, as in three cases in this series, an occurrence not unique for plasma cell myeloma, since it is recognized that in other diseases, such as lymphosarcoma, a considerable change must occur before lesions are demonstrated by x-ray.[3]

Marrow Findings: The ultimate diagnosis of plasma cell myeloma depends upon the finding of an increased number of large immature plasma cells in the marrow (figure 1). Without this finding the diagnosis is untenable. In this series 10 patients studied prior to 1938 had neither bone marrow aspirations nor bone marrow biopsies, the diagnosis being made on the basis of radiologic, chemical, hematologic and clinical findings. In nine instances the diagnosis was made by surgical biopsy of bone. Sternal marrow aspiration was performed in 32 instances. In 30 cases plasma cells accounted for 10 per cent or more of the marrow cells; in two patients, values of 4.0 and 4.2 per cent, respectively, were obtained.

It has been stated [4] that plasma cells may occur in the marrow of individuals not having plasma cell myeloma in numbers up to 23 per cent. The finding of an only slightly increased percentage of marrow plasma cells in two patients might therefore have been considered evidence against the diagnosis of plasma cell myeloma. In this connection three facts should be emphasized. First, in our experience, normal individuals have not been found to have more than 1 to 2 per cent plasma cells on marrow aspiration. Patients with certain chronic conditions such as tuberculosis, syphilis and carcinomatosis may have varying numbers of marrow plasma cells, not exceeding 10 per cent. Second, in those patients having increased number

of plasma cells in the marrow in association with disease other than plasma cell myeloma, the cells are small and mature in type. In patients with plasma cell myeloma, the majority of marrow plasma cells are large and immature, often containing two and occasionally more nuclei. Third, other significant laboratory data may be elicited so as to leave little doubt as to the diagnosis, as was the case in the two instances encountered in this series.

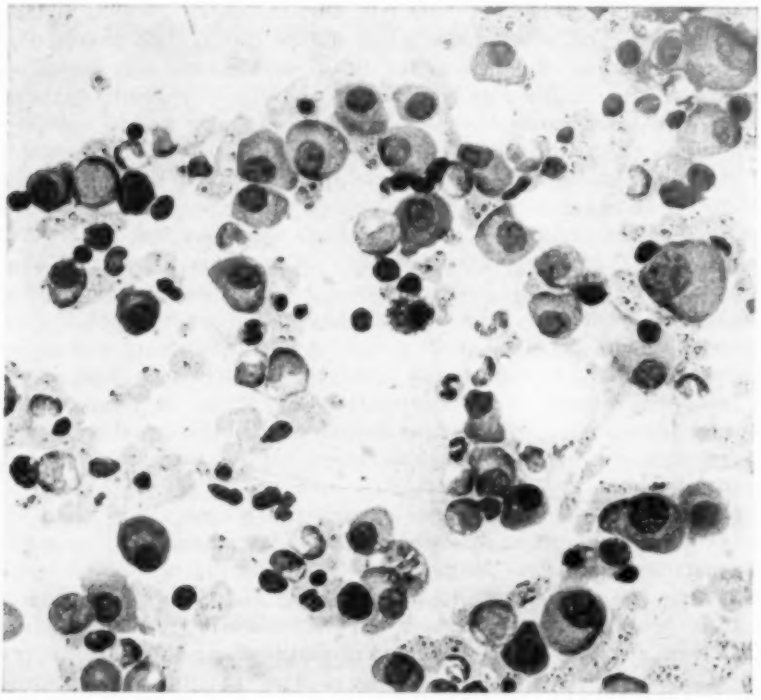


FIG. 1. Marrow aspiration smear showing increased numbers of large immature plasma cells from patient with plasma cell myeloma. ×976.

Hyperglobulinemia: Hyperglobulinemia is a common but not universal finding in plasma cell myeloma.[5] The serum globulin was determined in 49 patients. In 30 (61.2 per cent) the globulin was more than 4.0 gm. per 100 c.c. In six instances (12.3 per cent) it was between 3.0 and 4.0 gm. per 100 c.c. However, in 13 patients (26.5 per cent), the serum globulin was less than 3.0 gm. per 100 c.c. Therefore, a normal serum globulin does not eliminate the diagnosis of plasma cell myeloma. On the other hand, unexplained hyperglobulinemia should suggest the possibility of this disease.

Relationship of Percentage of Marrow Plasma Cells to Serum Globulin: It has been postulated that plasma cells are concerned with the production

of globulin.[6] If this were true, a direct correlation between the percentage of marrow plasma cells and the level of serum globulin might be found. No relationship could be demonstrated in these patients, however. A scattergram (figure 2), composed of the plasma globulin plotted against the percentage of marrow plasma cells in the 26 patients in whom these data were obtained, reveals that these points do not fall on a straight line, and thus indicates the lack of correlation between the two findings.

It should be recognized that the plasma cell determination is relative and represents only one site in the marrow. It is entirely possible that the plasma cell values thus obtained do not represent the true picture in any one patient.

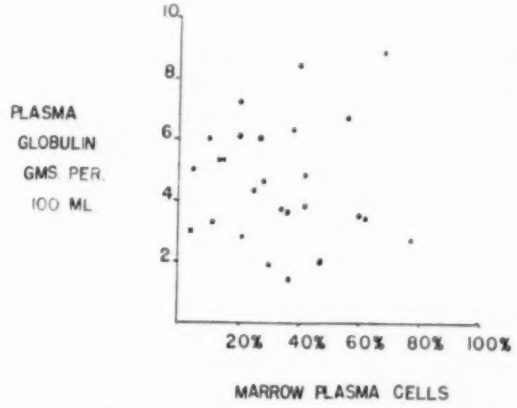


FIG. 2. Scattergram showing lack of correlation between plasma globulin level and percentage of marrow plasma cells (see text).

Bence-Jones Proteinuria: Bence-Jones proteinuria has long been known to be associated with plasma cell myeloma, although it is well recognized that it is not a constant or specific finding and may occur in a variety of other conditions in which bone marrow disease is usually present. Bence-Jones proteinuria was demonstrated in 13 of the 39 cases (33.3 per cent) examined for this finding. Serum globulin determinations were performed on 12 of these 13 patients, in nine of whom the globulin level was normal, whereas in three instances it was elevated above 3.5 gm. per 100 c.c.

In 25 cases Bence-Jones proteinuria was not demonstrated. Serum globulin determinations were done on 24 of these patients, in 20 of whom the globulin was elevated, and in only four instances was a normal value found. In one case, tests for Bence-Jones proteinuria were reported as "questionable." These findings are in accord with the statement[5] that Bence-Jones proteinuria is most often associated with normal globulin levels.

Hypercalcemia: Serum calcium determinations were made in 40 patients. Of these, 10 had values in excess of 11 mg. per 100 c.c. In contrast

to hyperparathyroidism with bone disease, however, the serum alkaline phosphatase is rarely if ever elevated in plasma cell myeloma.[7] In 22 instances in which the serum alkaline phosphatase was performed in this series it was within normal limits. The combination of an elevated serum calcium with a normal alkaline phosphatase in the presence of bone disease is worthy of emphasis, since it is seen rarely in any other disease entity and is of value in the diagnosis of plasma cell myeloma.

Hemorrhagic Phenomenon: Despite the fact that an unexplained hemorrhagic tendency is said to exist [8] in some patients with plasma cell myeloma, none of these patients exhibited this phenomenon.

Circulating Plasma Cells: Plasma cells may occur in small numbers in the peripheral blood of patients with plasma cell myeloma.[9] Circulating plasma cells are found far more frequently in plasma cell myeloma and rubella than in any other disease, and the differential diagnosis between these two entities is not difficult. In this group of patients, plasma cells were found in the peripheral blood in 16 instances, with values ranging from 1 to 26 per cent. The finding of plasma cells in the peripheral blood should be considered an indication for marrow aspiration to ascertain the presence of plasma cell myeloma, unless another explanation is obvious. On the other hand, failure to find plasma cells in the peripheral blood does not mitigate against a diagnosis of plasma cell myeloma, since they are not readily demonstrable in a majority of the cases.

Amyloidosis: Of this group of 51 patients, autopsy was performed in 16 instances. The diagnosis of plasma cell myeloma was confirmed in each case. Amyloidosis was found in only one patient. Although the occurrence of amyloidosis as a complication of plasma cell myeloma has long been recognized, the frequency with which it occurs is probably very low.

Renal Insufficiency: Renal failure is a well known complication of plasma cell myeloma. Decreased kidney function was apparent in 13 instances (25.5 per cent) in this series. Clinical data on these 13 patients are presented in table 4. A study of these cases reveals certain correlations which previously have received little comment.

As mentioned before, 10 of the 40 patients examined had elevated serum calcium levels of more than 11 mg. per 100 c.c. Of these 10 patients, there were 7 with renal insufficiency. A combination of hypercalcemia and renal insufficiency is unusual, since cases of uremia are usually associated with low serum calcium levels,[10] unless the renal failure is secondary to hyperparathyroidism, metastatic bone disease or vitamin D poisoning.

The ionized calcium is of greater physiologic significance than the total blood calcium content.[11] In nine of the 13 patients with renal insufficiency, total calcium, albumin and globulin were determined. In every instance the ionized calcium level was above the normal of 4.5 to 5.5 mg. per 100 ml. of serum. This was calculated from the formula:

$$\Delta \text{Ca} = 0.639\,\Delta \text{A} + 0.435\,\Delta \text{G}$$ [12]

TABLE IV

Renal Insufficiency in Plasma Cell Myeloma

Case No.	Serum Calcium (mg. per 100 ml.)	Ionized Calcium (mg. per 100 ml.)	Serum Phos. (mg. per 100 ml.)	Serum Albumin (gm. per 100 ml.)	Serum Globulin (gm. per 100 ml.)	Serum Urea Nitrogen (gm. per 100 ml.)	Maximal Urine Specific Gravity	Urea Clearance Per Cent	P.S.P. 2 Hour Excretion Normal	Bence-Jones Proteinuria	Serum Creatinine (mg. per 100 ml.)	B.P. in mm. Mercury	Died in Renal Insufficiency	Albuminuria
1	—	—	—	4.04	2.85	83.0	1.011	—	—	Neg.	—	175/100	Yes	2+
2	13.0	8.51	7.7	5.07	2.87	109.0	1.012		<15%	Pos.	12.0	158/78	Yes	4+
3	11.3	7.88	6.6	3.67	2.46	61.5	1.018	1.9%	—	Pos.	6.0	120/60	Yes	4+
4	10.8	6.99	14.2	3.68	3.55	177.0	1.018	—	—	Pos.	—	90/60	Yes	1+
5	9.1	6.00	6.5	1.60	4.80	36.0	1.017	27.0%	< 5%	Neg.	8.7	160/90	Unknown	4+
6	13.0	—	—	—	—	107.0	1.014	—	15%	Pos.	8.6	130/70	Yes	4+
7	12.1	8.60	3.8	4.29	2.32	48.0	1.014	17.8%	—	Neg.	4.8	145/75	Unknown	2+
8	15.4	11.50	5.2	3.10	4.30	74.0	1.008	—	—	Not done	3.3	140/60	Yes	1+
9	10.7	7.34	4.2	4.30	1.40	42.0	1.017	37.0%	—	Pos.	—	125/60	Unknown	2+
10	—	—	7.6	3.20	5.30	45.0	1.020	—	—	?	—	150/80	Yes	3+
11	11.5	6.80	4.4	3.40	4.60	26.0	1.015	—	—	Pos.	2.5	150/80	Unknown	4+
12	—	—	7.2	3.87	3.47	112.5	1.009	5.9%	—	Pos.	—	150/80	Yes	2+
13	12.6	9.24	6.0	4.40	2.00	66.0	1.013	—	—	Pos.	9.0	190/90	Yes	3+

where Δ Ca is the protein-bound calcium in milligrams per 100 c.c., Δ A the serum albumin in grams per 100 c.c., and Δ G the serum globulin in grams per 100 c.c. Total calcium minus protein-bound calcium is the ionized calcium level. In this series, therefore, in every instance where the data permitted the calculation to be made, renal insufficiency was associated with a high serum level of ionized calcium.

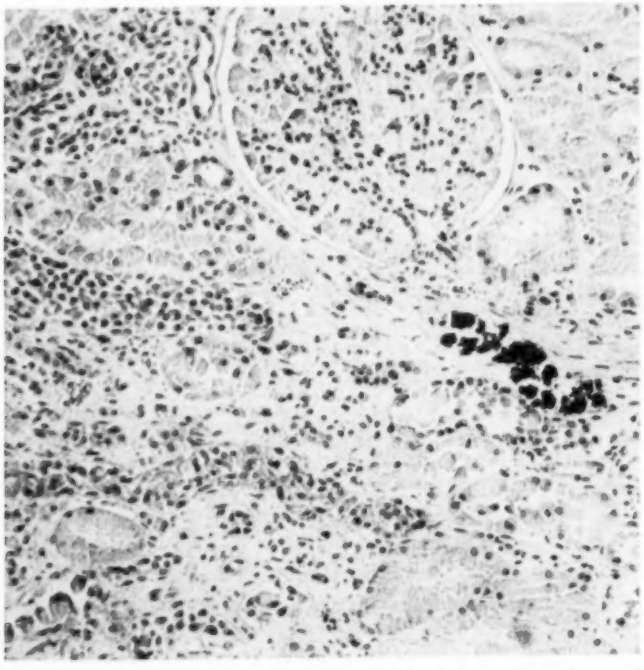


FIG. 3. Photomicrograph of kidney from a patient with plasma cell myeloma who died in uremia, showing calcium casts in the tubules. × 100.

As noted previously, 30 of the 49 patients had serum globulin levels above 4.0 gm. per 100 c.c., six patients had values between 3.0 and 4.0 gm. per 100 c.c., and 13 had values less than 3.0 gm. per 100 c.c. Of the 30 patients with elevated serum globulin, only four had renal insufficiency. Of the six patients with globulin levels between 3.0 and 4.0 gm. per 100 c.c., two had renal insufficiency. On the other hand, of the 13 patients with globulin levels under 3.0 gm. per 100 c.c., six had renal insufficiency. In other words, of the 12 patients with renal insufficiency in whom globulin determinations were done, only four had serum globulin levels above 4.0 gm. per 100 c.c., and these had a high content of serum ionized calcium. These data suggest that a normal or low globulin, in conjunction with a high level

of serum ionized calcium, is associated with renal failure in plasma cell myeloma.

Of the 13 patients in whom Bence-Jones proteinuria was demonstrated, eight had renal insufficiency. Furthermore, of the 13 cases of renal insufficiency, Bence-Jones proteinuria was demonstrable in eight. Adams and his associates [2] found 29 (47 per cent) of 62 patients demonstrated Bence-Jones proteinuria, and in only one of the 29 were the phenolsulfonphthalein excretion test and urea clearance normal. In this one exception it was stated that renal blood flow studies indicated nonfunction of 50 per cent of the renal units. These findings indicate that Bence-Jones proteinuria is more common in cases with renal insufficiency, and that its presence probably

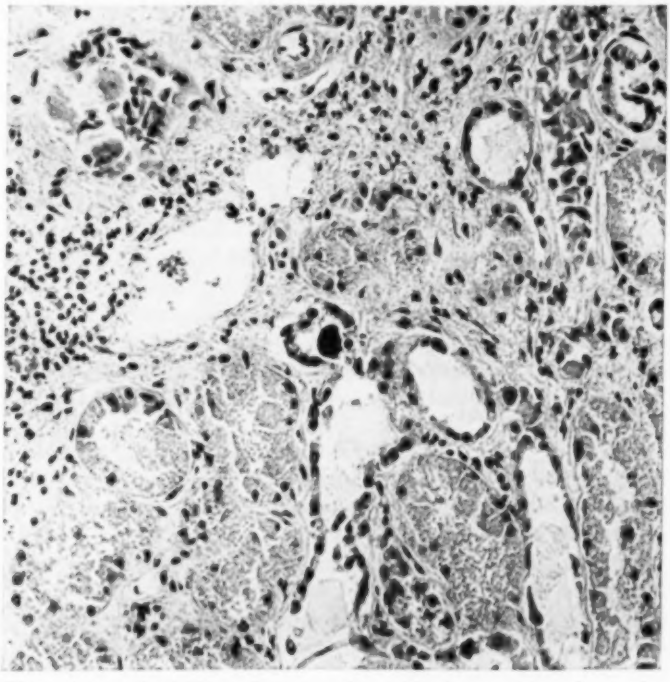


FIG. 4. Photomicrograph of kidney from a patient with plasma cell myeloma who died in uremia, showing calcium casts in the tubules. × 233.

forewarns of the onset of uremia. Microscopic examination of the kidneys of one of the patients with plasma cell myeloma who died in uremia showed calcium deposits in the tubules similar to those seen in the nephrocalcinotic kidney of hyperparathyroidism (figures 3 and 4). Since Bence-Jones protein injected experimentally into animals does not produce renal lesions, an interesting but as yet unproved speculation is that renal insufficiency of

plasma cell myeloma may be due to the combination in the tubules of Bence-Jones protein with ionized calcium to form an obstructive cast, with subsequent tubular destruction as a result of blockage of the lumen.

Treatment

Treatment of plasma cell myeloma remains unsatisfactory and inadequate. Roentgen therapy to bony lesions causing a localized or radicular type of pain usually affords temporary relief but does not affect the course of the disease.

Loge and Rundles [13] treated four patients with urethane (ethylcarbamate) for from eight to 10 weeks. Four grams daily in divided doses were used. In one patient leukopenia developed on the sixteenth day, at which time therapy was temporarily discontinued and smaller dosage subsequently instituted. In all patients symptomatic improvement occurred. In three patients there was a gradual improvement in blood values toward normal. In three cases repeated marrow aspirations at the termination of urethane therapy showed a marked decrease in the number of plasma cells, with a striking morphologic change in the plasma cells. In three cases a marked reduction in serum globulin occurred. Serial roentgen films over a period of months following urethane therapy showed no progression in the destructive skeletal lesions. In two cases it was believed that life was definitely prolonged. One patient was treated with 2 gm. of urethane daily for a period of 11 months, with complete relief of bone pain, increase in appetite and general well-being, a gain of six pounds in weight and a slight increase in the red cell count. No significant leukopenia was observed. A second patient treated similarly showed marked alleviation of bone pain but succumbed in uremia.

Our experience with urethane in this disease is limited. In doses of 2 to 3 gm. daily, nearly complete relief of bone pain uniformly occurs, and varying degrees of symptomatic improvement follow. No cases have been observed in which there was improvement in anemia or in which a reduction of serum globulin was found. With a few possible exceptions, it has been our impression that urethane did not alter the duration of the disease. Nevertheless, the symptomatic improvement, particularly alleviation of pain, is sufficiently striking in our opinion to make urethane of definite utility.

Thorne and associates [14] treated one patient with plasma cell myeloma with ACTH, 100 mg. daily for 21 days. Gain in weight and strength occurred. The globulin decreased from 10.2 gm. to 4.8 gm. per 100 c.c. An increase in hematocrit value, a rise in alkaline phosphatase and a progressive translucence of bony lesions occurred radiographically. There was a complete disappearance of plasma cells from the marrow at the end of therapy. Although our experience with ACTH and cortisone is limited, it is our belief that these drugs, with a few exceptions, do not alter the course of the disease. There may be symptomatic improvement, such as increase

in appetite and mild euphoria, which are usually a welcome reprieve from the previous apathy, anorexia and depression.

One patient with plasma cell myeloma and secondary acquired hemolytic anemia showed a striking improvement after ACTH was given for 30 days in a dosage of 20 mg. daily by slow intravenous drip in a mixture of 1,000 c.c. of 5 per cent dextrose and water. The erythrocyte count increased from 2,100,000 cells per cubic millimeter before treatment to 3,990,000 cells per cubic millimeter after therapy. The hematocrit value rose from 23 per cent to 42 per cent. The reticulocyte count fell from 13.2 per cent to 1.3 per cent, with a concomitant decrease in fecal urobilinogen excretion. The percentage of marrow plasma cells decreased from 34 to less than 2. There was marked symptomatic improvement during this course of therapy. However, four months after ACTH therapy the patient developed active pulmonary tuberculosis. The hemolytic anemia has not recurred. Dameshek and associates [15] treated three cases of acquired hemolytic anemia (secondary in two instances to lymphosarcoma and in one instance to chronic lymphatic leukemia) with ACTH. Nearly complete remission of the hemolytic process ensued, with marked clinical and laboratory improvement.

Duration

The duration of the disease from onset of symptoms until death was less than two years in 26 of the 29 cases followed to completion. Two patients lived three and one-half and five and one-half years, respectively. A third had a plasmacytoma involving a submental lymph node removed five years before death from disseminated plasma cell myeloma.

Discussion

The observations made on this group of 51 patients with plasma cell myeloma confirm, in general, those previously well established. The findings indicate, however, that certain features of the disease have not received enough emphasis.

The anemia, an almost constant finding, was macrocytic in more than half of the patients in whom laboratory data were extensive enough to allow this determination to be made. Both the anemia and macrocytosis are often of sufficient degree to suggest a diagnosis of pernicious anemia. The differential diagnosis is readily established by marrow aspiration in conjunction with appropriate roentgenologic and chemical studies.

Diffuse osteoporosis is common and, while more often found in conjunction with localized osteolytic lesions, may occur as the only roentgenologic abnormality. In our experience this fact has not been sufficiently appreciated.

A study of the patients having renal insufficiency indicates that renal failure tends to be associated with lower serum globulin levels, high values

of ionized calcium and Bence-Jones proteinuria. The pathogenesis of renal failure in plasma cell myeloma has not been elucidated. One of the most commonly accepted theories [16] is that tubular obstruction by protein casts causes a gradual cessation of function of nephrons, followed by progressive renal failure. The findings in these patients suggest that the high level of serum ionized calcium may have a causative relationship to the renal failure. An elevated blood calcium level is considered an important factor in nephrocalcinosis and renal failure in hyperparathyroidism.[7] One of the patients demonstrated nephrocalcinosis at autopsy. The increased incidence of Bence-Jones proteinuria in the patients with renal failure further suggests that a possible combination of this protein with ionized calcium present in increased amounts forms a tubular cast less resilient and more obstructive than the common protein cast. Although this is not proved by the data available, these concepts are worth further study.

Summary

The findings in 51 patients with plasma cell myeloma are presented. The age and sex incidence, marrow findings and incidence of hyperglobulinemia and Bence-Jones proteinuria agree in general with the established observations of many others.

The anemia was macrocytic in a high proportion of the patients, a fact which has received insufficient emphasis and which may lead to diagnostic error.

Diffuse osteoporosis is commonly present, usually associated with localized osteolytic lesions but occasionally as the sole evidence of bone involvement. Failure to appreciate this fact has led to incorrect diagnosis.

Renal failure in plasma cell myeloma tended to be associated with a normal or low serum globulin, high serum ionized calcium and Bence-Jones proteinuria. These findings may be considered of prognostic significance as regards renal failure. Their possible causative relationship to renal failure is discussed.

There is no satisfactory treatment. Therapy with roentgen irradiation will temporarily control local lesions. Urethane alleviates pain and causes marked symptomatic improvement in some patients. ACTH and cortisone therapy, with a few notable exceptions, has not seemed to alter the course of the disease.

BIBLIOGRAPHY

1. Wintrobe, M. M.: Clinical hematology, 1951, Lea and Febiger, Philadelphia.
2. Adams, W. S., Alling, E. L., and Lawrence, J. S.: Multiple myeloma, Am. J. Med. **6**: 141, 1949.
3. Jackson, H., and Parker, F.: Hodgkin's disease and allied disorders, 1947, Oxford University Press, New York.
4. Fadem, R. S., and McBirnie, J. E.: Plasmacytosis in diseases other than primary plasmacytic disease, Blood **5**: 191, 1950.

5. Stewart, A., and Weber, F. P.: Myelomatosis, Quart. J. Med. **7**: 211, 1938.
6. Bing, J.: Further investigations on hyperglobulinemia. II. Is serum globulin formed from plasma cells and reticulo-endothelial cells? Acta. med. Scandinav. **103**: 565, 1940.
7. Albright, F.: The parathyroid glands and metabolic bone disease, 1948, Williams and Wilkins Co., Baltimore.
8. Bayrd, E. D., and Heck, F. J.: Multiple myeloma—a review of 83 proven cases, J. A. M. A. **133**: 147, 1947.
9. Morisette, L., and Watkins, C. H.: Multiple myeloma, Proc. Staff Meet., Mayo Clin. **17**: 433, 1942.
10. Fishberg, A. M.: Hypertension and nephritis, 1944, Lea and Febiger, Philadelphia.
11. Duncan, G.: Diseases of metabolism, 1951, W. B. Saunders Co., Philadelphia.
12. Miller, M.: The diffusible calcium of serum and transudates in vivo, J. Biol. Chem. **122**: 71, 1937.
13. Loge, J. P., and Rundles, R. W.: Methane (ethyl carbamate) therapy in multiple myeloma, Blood **4**: 201, 1949.
14. Thorn, G. W., Forsham, P. H., Frawley, T. F., Hill, S. R., Jr., Roche, M., Stachelin, D., and Wilson, D. L.: The clinical usefulness of ACTH and cortisone, New England J. Med. **242**: 783, 1950.
15. Dameshek, W., Rosenthal, M. C., and Schwartz, L. I.: The treatment of acquired hemolytic anemia with adrenocorticotrophic hormone (ACTH), New England J. Med. **244**: 117, 1951.
16. Blackman, S. S., Jr., Barker, W. H., Buell, M. V., and Davis, B. D.: On the pathogenesis of renal failure associated with multiple myeloma. Electrophoretic and chemical analysis of protein in the urine and blood stream, J. Clin. Investigation **23**: 163, 1944.

CASE REPORTS

LARGE ANEURYSM IN THE ANTERIOR CRANIAL FOSSA: SUCCESSFUL REMOVAL WITH RECOVERY *

By Louis Odessky, M.D., *Brooklyn, N. Y.*, and David E. Fader, M.D., F.A.C.P., *Augusta, Georgia*

An aneurysm, apparently self-cured, situated in the left anterior cranial fossa and attached by a long narrow arterial stalk to the left internal carotid artery, was shelled out at operation, the patient making an uneventful recovery. This aneurysm simulated a tumor in that it was found far removed from the customary locations of intracranial aneurysms, caused only psychotic symptoms, and was larger than most aneurysms.

Case Report

A 34 year old white man was admitted to the hospital in a semicomatose condition on October 20, 1949. During the previous evening he had experienced his first convulsion (Jacksonian in type), which was followed by 17 subsequent similar convulsions up to the time he was brought to the hospital.

At the age of five years he had had several "seizures" of short duration. One year prior to admission the patient was hit by a truck and sustained fractures of the pelvis and one leg. During the past year the patient's behavior had undergone a noticeable change: where he had formerly been kind and courteous he was now very irritable and rude; where he had been very industrious and conscientious he was now neglectful. There were episodes of amnesia, increased drinking, aimless talking and suicidal threats. For several months prior to admission the patient complained of severe frontal headaches.

The examination on admission showed an acutely ill, semicomatose man who was sweating profusely. His blood pressure was 92 mm. of mercury systolic and 58 mm. of mercury diastolic. He reacted to obnoxious stimuli but not to the spoken inquiry. His pupils were widely dilated and reacted sluggishly. All reflexes were sluggish, and the patellar reflexes could not be obtained. The remainder of the physical examination was not notable. Two days later the patient appeared rather dull mentally, flattened emotionally, and somewhat confused. One week after he entered the hospital no abnormal reflexes were noted. A spinal puncture showed clear fluid, with an initial pressure of 148 mm. of water. Pressure over the right jugular vein caused an increase to 202 mm. of water, which fell rapidly to 140 mm. of water; pressure over the left jugular vein caused an increase to 152 mm. of water, which fell to 130 mm. of water.

The laboratory studies on the blood, urine and cerebrospinal fluid were all normal.

* Received for publication October 31, 1952.

From the Departments of Pathology and Medicine, Augusta Veterans Administration Hospital, Augusta, Georgia.

Sponsored by the Veterans Administration and published with the approval of the Chief Medical Director. The statements and conclusions published by the authors are a result of their own study and do not necessarily reflect the opinion or policy of the Veterans Administration.

A roentgenogram of the skull (figure 1) delineated an egg-shaped tumor, 4.0 by 3.5 cm., in the anterior fossa, barely to the left of the midline, which had a calcified periphery but did not show calcium in the remainder of the tumor mass. There was some evidence of eburnation, sclerosis and erosion of bones just anterior to the sella turcica. The pituitary fossa was of normal size. No erosion of the clinoid processes was apparent.

An electroencephalogram indicated a probable tumor in the left frontal region.

The differential diagnoses were: (1) echinococcus cyst; (2) aneurysm; (3) craniopharyngioma.

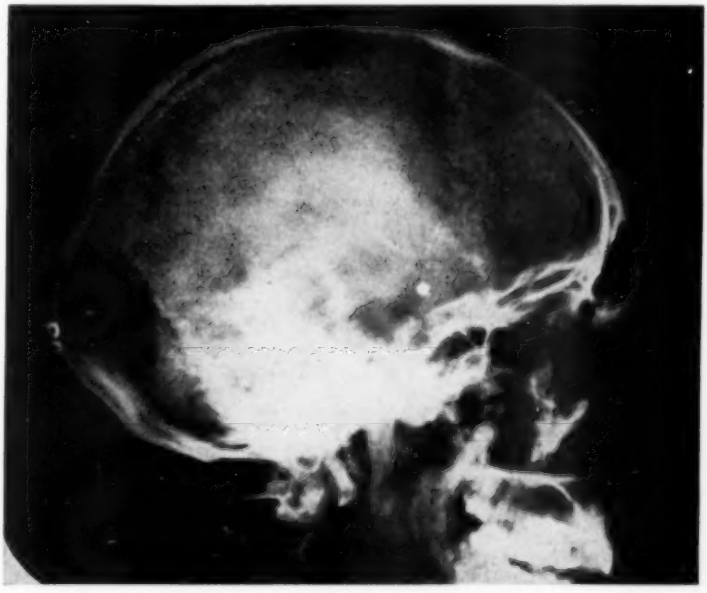


FIG. 1. Roentgenogram of the skull. The white dot is on the periphery which delineates the boundary of the calcified mass in the anterior fossa.

Craniotomy, performed on November 7, exposed a tumor the size of a small egg, greenish in color and exhibiting calcified areas; it was removed by finger dissection. There was a sudden spurt of blood, immediately controlled with clips. At this time it could be seen that the tumor was attached from the left side of the sella turcica. The patient's recovery was uneventful.

Following the operation the patient was pleasant, agreeable and coöperative at all times. Mentally he was dull, displaying very little interest in what was happening around him. Speech was relevant and coherent. At home he did only odd jobs, being unable to do any productive work. A year after the craniotomy was performed the patient stated that he had not experienced any headaches since the operation. To the examining physician he appeared more alert but retained the emotional flatness.

Pathologic Findings:

Gross: The specimen consisted of an ovoid aneurysm and several fragments of brain tissue fixed in formalin. The aneurysm was resilient and measured 4.0 by 3.5 by 3.0 cm. Its surface was smooth for the most part, but contained irregular,

flat, raised, calcified plaques varying from 1 mm. to 10 mm. in diameter. Also on its surface was a circular aperture, 2 mm. in diameter, which was the stump of an artery. The wall of the aneurysm was 0.5 to 1 mm. in thickness, and the cavity was filled with a firm, reddish brown, granular thrombus which crumbled easily (figure 2). Between the wall of the aneurysm and the thrombus, adjacent to the aperture, there was a 4 mm. wide dark red zone of semifluid blood. The brain tissue from the frontal lobe weighed 30 gm. Both the gray and the white matter contained ecchymoses.

FIG. 2. The aneurysmal sac is filled with a thrombus composed of disintegrated and crumbled old blood. The marker points to the very limited space into which blood flowed from the contiguous artery.

Microscopic: Representative sections from various blocks of the aneurysm revealed, adherent to the intima, clumps of fibrin, platelets and red blood cells, many of which had disintegrated and many of which had remained intact. The intima was hyalinized and contained deposits of calcium, while the subintimal zone was distended with xanthoma cells. The media consisted of laminated collagenous connective tissue with flattened cells and pyknotic nuclei. Within the adventitia and on its surface were clumps of old blood pigment and scattered intact red blood cells. The surface was also lined with a thin layer of lymphocytes. Prepared sections of the brain showed hemorrhages distributed throughout the gray matter, the white matter (including the spaces of Virchow-Robin), and the meninges. The cortex disclosed ganglion cells in various stages of chromatolysis, and the white matter showed a moderate increase in the number of glial cells.

DISCUSSION

This large aneurysm, located in the left anterior cranial fossa beneath the left frontal lobe, produced only generalized symptoms attributable to the com-

pression and distortion of the brain substance and to the presence of extravasated blood in this area. These symptoms consisted of headaches, convulsive seizures, amnesia, mental dullness and irritability bordering on psychosis, and indicated the diagnosis of tumefaction. A case with features somewhat similar to this one was that of an aneurysm of a primary branch of the left anterior cerebral artery in the left frontal lobe, described by Booth [2] in 1909. In addition to headache, mental apathy, slowness of speech and convulsive seizures, Booth's patient had stiffness of the neck, tenderness at the base, and optic neuritis with choking of the discs. A diagnosis of a tumor of the frontal lobe was made. One month later the aneurysm ruptured and the patient died.

In the authors' case the presence of a space-occupying lesion was revealed in a roentgenogram of the skull (figure 1). The ovoid aneurysm was outlined by the thin layer of calcification along its periphery. Generally, the extent of calcification visible roentgenographically depends on the quantity and distribution of the calcium deposition. Consequently, many aneurysms are not seen in x-rays because the density of the calcium deposits is insufficient for definition. Thus, various observers have reported percentages that differ greatly. Dyke [5] stated that in his series a high percentage showed calcification (87 per cent), while Dandy reported only 15 per cent. When aneurysms are apparent in x-rays they can be identified by the roentgenologic criteria which have been carefully described by Sosman and Vogt,[11] Dyke,[5] Jefferson[8, 9] and Dandy [3]—particularly aneurysms of the internal carotid artery. Angiography has often been used to aid in the visualization and identification of these aneurysms; however, the authors are doubtful that the injection of a radiopaque medium would have been of any help in their case, since the quantity of blood that could seep into the almost occluded aneurysm was insufficient to carry enough radiopaque substance to be visualized on x-ray (figure 2). For that matter, neither the Matas test nor the ligation of the carotid artery in the neck would have been of any value as a preliminary procedure in this case.

From the description of the operation it may be concluded that the aneurysm arose from the terminal end of a long, narrow anomalous branch of an artery adjacent to the left side of the sella turcica. The anterior cerebral artery arises from the internal carotid artery and runs in the longitudinal fissure but does not give off any significant branches to the inferior surface of the frontal lobe. The middle cerebral artery is a continuation of the internal carotid artery and gives off some small branches to the inferior surface of the frontal lobe; however, these branches are a considerable distance from the sella turcica. Therefore, it may be inferred that the aneurysm developed in an anomalous offshoot of the internal carotid artery.

The size of the aneurysm (4.0 by 3.5 by 3.0 cm.) is noteworthy. Several intracranial aneurysms of comparable or greater size have been reported at times but their percentage is very low—about 5 per cent of all intracranial aneurysms reported. An extensive series of such large aneurysms, some of which were enormous, was collected by Beadles [1] from the Royal College of Surgeons. More recently, Jefferson [8] gathered 13 such cases from the literature.

Aneurysms are apparently self-cured where the sac becomes thrombosed. When, in turn, the thrombus becomes organized so that the sac is fibrosed and cordlike, a complete and permanent cure results. Several such cured aneu-

rysms have been reported in the literature. Hermann et al.[8] discovered an aneurysm of the anterior communicating artery which evolved into a small nodule of solid fibrous tissue surrounded by a large empty space after causing homonymous hemianopsia and great enlargement of the sella turcica in a patient who died of multiple cerebral thromboses two years after the authors first saw him. Dandy [4] observed one case of an aneurysmal sac which was completely filled with a thrombus and was embedded in the third nerve. It was an aneurysm of the right internal carotid artery at the junction of the posterior cerebral arising in the position of the posterior communicating. The patient died of a ruptured arteriovenous aneurysm in the occipital lobe on the opposite side. A large aneurysm (the size of a small tangerine) of the right cerebral artery was seen by Lyall [10] in a necropsy of a man who had died in a street car accident. The aneurysm was completely thrombosed and also contained calcareous deposits. In 1875, Hutchinson [7] described an aneurysm (the size of a bantam's egg) of the internal carotid artery which had undergone a spontaneous cure. The presence of the aneurysm was diagnosed 11 years prior to the death of the patient, who succumbed to a pelvic abscess.

Many other aneurysms, of which the authors' case is an example, become almost wholly filled with a thrombus which does not organize but remains a dark red laminated clot that crumbles easily. A potential space remains between the thrombus and the wall of the artery into which the blood slowly diffuses. Thus the sac keeps on expanding, but at a slow rate, since the arterial pressure of the blood upon the aneurysmal wall is greatly reduced by the damping action of the thrombus at the inlet of the aneurysm. This was demonstrated in the authors' case in the gross specimen by the dark red zone between the thrombus and the aneurysmal wall, and in the histologic sections by a mass of blood in the same region. That the leakage from the thrombosed aneurysm was of long duration and continued up to the time of the operation was borne out by the presence of old blood pigment as well as recent hemorrhages in the adventitia of the aneurysm and the fresh blood in the adjacent meninges and the brain. A thrombus may thus effect a seeming cure, but the aneurysm may go on to eventual rupture.

Summary

A large, almost completely thrombosed aneurysm located in the left anterior cranial fossa, which arose in an anomalous branch of the internal carotid artery, produced only psychotic symptoms. Neither angiography, the Matas test, nor ligation of the carotid artery in the neck would have been useful in diagnosing this case. The aneurysm was shelled out at operation; the patient made an excellent and uneventful recovery. The pathologic aspects of the aneurysm were discussed. Only four other cases of completely thrombosed intracranial aneurysms were found in the literature. In all these cases the long-term prognosis was favorable.

BIBLIOGRAPHY

1. Beadles, C. F.: Aneurisms of the larger cerebral arteries, Brain **30**: 285-336, 1907.
2. Booth, J. A.: An aneurysm of the left anterior cerebral artery with rupture, simulating a brain tumor, J. Nerv. and Ment. Dis. **36**: 528-533, 1909.

3. Dandy, W. E.: Intracranial arterial aneurysms, Ithaca, New York, Comstock Publishing Co., Inc., Cornell University, 1944, p. 16.
4. See reference 3, Table B, Case XIX, and p. 9.
5. Dyke, C. G., *in* McKinney, J. McD., Acree, T., and Soltz, S. E.: The syndrome of the unruptured aneurysm of the intracranial portion of the internal carotid artery, Bull. Neurol. Inst. New York **5**: 247–277, 1936.
6. Hermann, K., Obrador, S., and Dott, N. M.: Intracranial aneurysms and allied clinical syndromes: cerebral arteriography in their management, Lisboa méd. **14**: 782–814, 1937.
7. Hutchinson, J.: Aneurism of the internal carotid within the skull diagnosed eleven years before the patient's death. Spontaneous cure, Tr. Clin. Soc. London **8**: 127–131, 1875.
8. Jefferson, G.: Compression of the chiasma, optic nerves, and optic tracts by intracranial aneurysms, Brain **60**: 444–497, 1937.
9. Jefferson, G.: On the saccular aneurysms of the internal carotid artery in the cavernous sinus, Brit. J. Surg. **26**: 267–302, 1938–1939.
10. Lyall, A.: Large aneurysm of the circle of Willis with spontaneous cure by thrombosis, Brit. M. J. **2**: 282, 1936.
11. Sosman, M. C., and Vogt, E. C.: Aneurysms of the internal carotid artery and the circle of Willis, from a roentgenological viewpoint, Am. J. Roentgenol. **15**: 122–134, 1926.

OCCURRENCE OF INFECTIOUS MONONUCLEOSIS AND SYPHILIS IN THE SAME INDIVIDUAL * †

By C. J. D. Zarafonetis, M.D., F.A.C.P., *Philadelphia, Pennsylvania*

Infectious mononucleosis and syphilis are notable for their widely varied clinical manifestations. It is also recognized that the differential diagnosis between these conditions may be very difficult under certain circumstances. This is readily apparent when it is recalled that malaise, lassitude, headache, myalgia, fever, sore throat, generalized lymphadenopathy and skin rash are features common to infectious mononucleosis and secondary syphilis. Fortunately, differentiation is usually possible through the use of appropriate laboratory studies. These include repeated examinations of the blood for the appearance of the leukocyte changes associated with infectious mononucleosis, and serial heterophil agglutination tests to detect agglutinins for sheep erythrocytes, which characteristically develop in increasing titer during the course of this disease. With these tests the diagnosis of infectious mononucleosis may be established or ruled out. In the presence of infectious mononucleosis, however, the diagnosis of syphilis by conventional serologic tests is complicated by the fact that positive reactions for syphilis may also occur in the former disorder. Usually the problem is resolved upon careful analysis of the history and findings existing prior to the onset of infectious mononucleosis, and by follow-up serologic tests. The positive reactions due to infectious mononucleosis often persist only a week or two, although in rare instances it has required as long as three months for the patient's serum to become negative.[1-5]

* Received for publication November 5, 1952.
From the Departments of Internal Medicine, University of Michigan Medical School and Temple University Medical School.
† Part of a broader study of infectious mononucleosis made possible by a grant from the Charles Stewart Mott Foundation.

Thus, while there may be confusion regarding the possibility of coexisting infectious mononucleosis and syphilis, it is usually temporary. During the course of an extensive investigation of infectious mononucleosis, however, a clinical problem was encountered which required prolonged study before both diagnoses were established. The purpose of this report is to record this unique and instructive case.

Case Report

A 17 year old colored female camp counselor was admitted to the University of Michigan Hospital on July 5, 1946. Although she had noticed enlarged, tender nodes in her neck for about nine days, she had been otherwise asymptomatic until two days before admission. At that time she experienced the onset of headache, sore throat and difficulty in swallowing. These symptoms gradually increased in severity and were unrelieved by aspirin. Because of increasing malaise and feverishness, she was referred to the hospital. Her past history was noncontributory.

Upon examination she appeared acutely ill. The temperature was 101° F., the pulse, 96 beats per minute, and the blood pressure, 108/64 mm. of Hg. The skin was clear. Positive findings included ulcerative, fiery red lesions on the pharynx and both tonsillar pillars. There was also generalized lymphadenopathy, with discrete, soft, tender multiple nodes, 2 to 3 cm. in diameter, not only in the cervical triangles but in the axillae and inguinal regions as well. There was no pain or stiffness of the neck. No abnormalities were found in the chest. Tenderness was elicited in the left upper quadrant of the abdomen, but the spleen was not felt. The neurologic findings were within normal limits.

The white blood cell count was 9,100 per cubic millimeter. The intern's working diagnosis was "probable infectious mononucleosis." Because of the late hour (midnight), other studies were deferred. The patient was given 0.65 gm. acetylsalicylic acid, and treatment with aqueous penicillin was started at a dosage schedule of 30,000 units intramuscularly every three hours.

On the following morning a generalized eruption appeared which was most prominent on the extremities. The lesions were erythematous, maculopapular and nonpruritic. The spleen was palpable about 5 cm. below the costal margin on deep inspiration and was tender. The findings were otherwise unchanged from the examination on admission. Because of the eruption, penicillin was discontinued after the patient had received a total of 150,000 units. Sulfadiazine therapy was then started and continued for the next four days at a dose of 1 gm. every four hours.

Laboratory studies at this time revealed the hemoglobin to be 11.9 gm. (76 per cent); the leukocytes numbered 7,650 per cubic millimeter. The differential count was as follows: neutrophils, 54 per cent; lymphocytes, 30 per cent; monocytes, 15 per cent, and basophils, 1 per cent. The Kahn test on the blood serum was positive in a titer of 40 units. The heterophil agglutination reaction was positive in serum dilutions up to 1:512. Examination of the urine was negative.

Course in hospital: Within three days the patient was afebrile, the eruption had disappeared, and there was general symptomatic improvement. However, on July 10 she developed pain in the left calf and weakness in the left quadriceps muscle. There were no reflex changes. The temperature was normal. A lumbar puncture showed the spinal fluid to be clear, and the pressure and fluid dynamics were normal. The cell count revealed a single cell. The Pandy and the Nonne-Apelt tests were negative. Total protein was 20 mg. per cent. The colloidal gold curve was read 0000000000 and the gum mastic curve 000000. Both the Kahn standard and the Kahn supersensitive tests were negative.

During the next five days the pain and muscular weakness subsided and the patient became asymptomatic.

The Kahn test had been repeated on July 13 and was again positive. This time the titer was 80 units, and the Kahn verification procedure indicated that the reaction was luetic. The patient was carefully questioned regarding possible exposure and denied ever having had sexual contact. Pelvic examination revealed normal external genitalia. The introitus was virginal, with the hymen intact. There were no scars or lesions, and there was no discharge. The rectal examination was also negative.

It was concluded that the positive tests for syphilis were probably due to infectious mononucleosis. The situation was explained to the patient and she was advised to return for follow-up study, including serologic tests. Subsequent physical findings were within normal limits. The blood counts are summarized in table 1, the results of the serial heterophil agglutination tests[6, 7] and of the serologic tests for syphilis in table 2.

TABLE 1

Total Leukocyte and Differential Counts

Date	Day of Disease*	Leukocytes per Cu. Mm.	Differential Count in Per Cent:				
			Neutrophils	Lymphocytes	Monocytes	Eosinophils	Basophils
7-5-46	9	9,100	—	—	—	—	—
7-6-46	10	7,650	54	30	15	0	1
7-11-46	15	6,000	56	37	3	4	0
7-16-46	20	6,400	41	45	8	5	0‡
7-31-46	35	6,700	53	42(16)†	5	0	3
8-21-46	56	8,900	63	29(7)	3	2	0
9-4-46	70	6,750	57	37(6)	6	0	0
11-16-46	143	6,600	74	22(7)	3	1	0
3-1-47	248	8,900	76	18(6)	5	1	0

* Day from onset of acute illness.

† Figures in parentheses denote proportion of atypical lymphocytes of infectious mononucleosis type.

‡ Plus 1% plasma cells.

As can be seen from the data recorded in table 2, the patient's serum was still positive in tests for syphilis on May 31, 1947, almost a year after the acute illness. Despite the absence of a history of venereal contact, it was reasoned that the patient had syphilis which required treatment. Arrangements were made, therefore, with the Michigan Rapid Treatment Center in Ann Arbor, and the patient was admitted for therapy on August 15, 1947. An independent examination was, of course, done by the physician in charge. The history was again negative in all respects. Physical examination failed to reveal a primary lesion or scar. There was no evidence of eruption, alopecia, leukoderma colli, or condylomata lata or acuminata. The eyes, nose, teeth and mucous membranes were normal. The chest and abdomen were negative. There were no abnormalities of the genitalia. The outlet was virginal. The neurologic examination was negative. The serologic tests for syphilis were positive, as is indicated in table 2. However, examination of the spinal fluid at this time revealed normal findings, including negative Kahn and complement-fixation tests. The diagnosis was late latent syphilis, and the patient received 2,400,000 units of penicillin over a 10 day period. She was discharged on August 26, 1947.

The follow-up serologic tests are also shown in table 2. Sixty-five days after

TABLE II

Results of Heterophil Agglutination Tests and Serologic Tests for Syphilis on Sera

Date	Day of Disease‡	Heterophil Agglut. Titer	Kahn (units)	Mazzini (units)	Mazzini Cardiolipin (units)	Kline Cardiolipin (units)	Kline Exclusion (units)	Kolmer Comp. Fix. (units)	Cardiolipin Comp. Fix. (units)
7-6-46	10	1/512	40	64	112	224	—	Anticomp.	Anticomp.
7-13-46	17	1/512	80	64	112	224	—	48	224
7-16-46	20	1/256	80	—	—	—	—	—	—
7-31-46	35	1/128	80	40	56	112	—	32	224
8-14-46	49	1/64	40	48	48	128	—	36	224
8-21-46	56	1/32	40	—	—	—	—	—	—
9-4-46	70	1/32	160	64	48	224	—	48	224
10-12-46	108	1/8	160	72	72	192	—	Anticomp.	Anticomp.
11-16-46	143	1/8	160	Negative	Negative	Negative	—	4	‡
3-1-47§	248	0	600	96	96	144	192	256	256
5-31-47	339	0	400	72	56	104	96	112	384
8-15-47**	415	—	Positive*	—	—	—	—	Positive*	—
8-19-47	419	—	Positive*	—	—	—	—	—	—
10-30-47	487	—	Positive†	—	—	—	—	—	—
3-3-48	612	—	Doubtful†	—	—	—	—	—	—
5-10-48	680	—	Negative†	—	—	—	—	—	—
5-27-48	697	—	Negative†	—	—	—	—	—	—
6-1-50	4 yrs.	0	Negative	—	—	—	—	Negative	—

The Kahn tests were performed by Dr. Reuben Kahn unless otherwise noted. Results marked with an asterisk (*) were obtained at the Michigan Rapid Treatment Center, Ann Arbor, while those marked with a dagger (†) were performed at the Wayne University Health Service. All other tests for syphilis were performed in the laboratory of Dr. Charles R. Rein, New York.

‡ Day of disease calculated from time of onset of symptoms.

§ The Neurath procedure was also performed on this specimen and was positive for syphilis.

** Date patient admitted to Michigan Rapid Treatment Center for antiluetic therapy.

completion of treatment the Kahn test was still positive. After 190 days a plus-minus doubtful reaction was obtained, but all subsequent tests were negative.

COMMENT

It is possible to state in retrospect that this patient had both infectious mononucleosis and syphilis. At the time of admission to the hospital the clinical findings were compatible with either diagnosis, and may have been due to either or both disorders. Interpretation of the eruption was complicated by the administration of penicillin, since it could represent a Jarisch-Herxheimer reaction as well as an exanthem of infectious mononucleosis. The serial heterophil agglutination tests and repeated hematologic examinations established the diagnosis of infectious mononucleosis relatively early in the course of study. The major problem was that of proper evaluation of the positive serologic tests for syphilis. During the first eight weeks, as can be seen in table 2, the Kahn tests showed an initial increase in titer, followed by a fall. This would be the expected curve if the positive results were due to infectious mononucleosis.[1-5] On the other hand, the patient had received 150,000 units of penicillin on the day of admission, and it was also possible that the fall in the Kahn test titers reflected temporary suppression of an acute luetic process. That the latter interpretation was correct seems evident from the subsequent rebound in titers of the Kahn and other tests for syphilis (table 2). The attainment of negative serology only after adequate antiluetic therapy is further evidence in support of this conclusion. It is of interest, however, that while

the diagnosis of syphilis appears to be established, there is no satisfactory explanation as to the source of infection and the manner in which it was acquired.

Previous reports dealing with the clinical association of these two diseases have been largely concerned with the development of infectious mononucleosis in individuals under treatment for syphilis.[8, 9] There have also been described isolated instances where the diagnosis of syphilis was made because of clinical and laboratory findings existing prior to the occurrence of infectious mononucleosis.[10, 11]

In view of the chronicity of syphilis, it is not surprising that an occasional untreated luetic has developed superimposed infectious mononucleosis. The likelihood of the converse situation is more remote, however, since infectious mononucleosis runs a relatively short course. Indeed, the close relationship of the two conditions in this patient, as judged from the clinical and laboratory findings, appears to be unique.

Summary

The apparently simultaneous occurrence of infectious mononucleosis and syphilis in a 17 year old girl is reported, and the difficulties attendant to establishing the latter diagnosis are discussed.

Acknowledgments

Grateful appreciation is expressed to Dr. Reuben Kahn and Dr. Charles R. Rein for their coöperation in performing serologic tests for syphilis on the specimens obtained from this patient.

BIBLIOGRAPHY

1. Kahn, R. L.: Are there paradoxic serologic reactions in syphilis? Arch. Dermat. and Syph. **39**: 92, 1939.
2. Bernstein, A.: Infectious mononucleosis, Medicine **19**: 85, 1940.
3. Kaufman, R. E.: False positive reactions for syphilis in infectious mononucleosis, J. Lab. and Clin. Med. **26**: 1439, 1941.
4. Wechsler, H. F., Rosenblum, A. H., and Sills, C. T.: Infectious mononucleosis: report of an epidemic in an Army post, Ann. Int. Med. **25**: 113, 1946.
5. Zarafonetis, C. J. D., and Kent, J. F.: Serologic tests for syphilis in infectious mononucleosis, to be published.
6. Zarafonetis, C. J. D.: Infectious mononucleosis, Journal-Lancet **69**: 364, 1949.
7. Zarafonetis, C. J. D., and Oster, H. L.: Heterophile agglutination variability of erythrocytes from different sheep, J. Lab. and Clin. Med. **36**: 283, 1950.
8. Baldridge, C. W., Rohner, E. J., and Hansmann, G. H.: Glandular fever (infectious mononucleosis), Arch. Int. Med. **38**: 413, 1926.
9. White, E. C.: Lymphadenosis, an acute benign disease simulating acute leukemia, U. S. Nav. M. Bull. **22**: 302, 1925.
10. Farley, D. L.: Acute infectious mononucleosis, M. Clin. North America **21**: 1139, 1937.
11. Gendel, B. R., and Cottrell, J. E.: Infectious mononucleosis: a review, Am. Pract. **2**: 472, 1948.

THE USE OF ACTH IN INFECTIOUS MONONUCLEOSIS*

By JOSEPH K. DORAN, M.D., and AUSTIN S. WEISBERGER, M.D.,
Cleveland, Ohio

INFECTIOUS mononucleosis is usually a benign, self-limited disease of unknown etiology, requiring only symptomatic therapy. Occasionally, serious complications such as hepatitis, thrombocytopenia, myocarditis, central nervous system involvement and splenic rupture may develop. Several fatal cases have been described, with death due to splenic rupture or to central nervous system involvement.[1, 2] Attempts to modify the course of the disease with sulfonamides,[3] penicillin,[3] aureomycin [4, 5] or chloramphenicol [3] have been unsuccessful. In view of the pathologic findings of widespread involvement of almost every organ in the body by perivascular infiltration of normal and abnormal lymphocytes with enlargement of the lymph nodes and spleen,[6] ACTH or cortisone might be expected to be beneficial. To our knowledge, no report of the use of these compounds in treating the more serious complications of infectious mononucleosis has appeared in the literature. The following report deals with a case of infectious mononucleosis showing severe liver disease, azotemia, thrombocytopenia and a toxic course in which striking improvement accompanied the use of ACTH.

CASE REPORT

An 18 year old white male was admitted to the University Hospitals of Cleveland with a chief complaint of fever and headache. Seven days prior to admission he noted frontal headache. Five days before admission he developed general malaise, diffuse myalgia, fever, chills, nausea, vomiting, a mild sore throat and nasal congestion. At approximately the same time he developed visible enlargement of the cervical lymph nodes, which were tender and painful. The temperature remained elevated and fluctuated between 100° F. and 104° F. He had two episodes of nasal bleeding. He was treated with aureomycin for four days and with penicillin for two days, without improvement. On the day prior to admission a yellow tinge was noted in his skin.

The past history was of importance in that as a child he had had jaundice for which he was kept in bed for one month. He was also said to have had facial edema as a child and a diagnosis of kidney disease was made. No further information in regard to the diagnosis of hepatic or renal disease was available.

On physical examination the temperature was 40° C., the blood pressure 160/95 mm. of Hg, the pulse 112, and the respirations 20 per minute. The patient was a well developed and well nourished, acutely ill young male. There was a diffuse erythematous flush over the cheeks and forehead, and an urticarial eruption was present over the trunk. The skin and sclerae were icteric and the conjunctivae were inflamed. Several tender, 2 cm. by 2 cm., movable soft lymph nodes were present in the posterior cervical region bilaterally. A large (3 cm. by 4 cm.) tender lymph node was present in the right submandibular region. Small axillary and inguinal nodes were palpable. The soft palate and pharynx were diffusely red, and several tiny hemorrhagic areas were present. Examination of the heart and lungs was negative. The abdomen was tense and diffusely tender. The liver and spleen were thought to be enlarged but

* Received for publication July 21, 1952.
From the School of Medicine, Western Reserve University, and Department of Internal Medicine, University Hospitals, Cleveland, Ohio.

could not be delineated because of the diffuse tenderness and spasm. There was bilateral costovertebral angle tenderness.

Laboratory Findings: The important laboratory findings are summarized in table 1. On admission the hemoglobin was 14.1 gm., the erythrocyte count 4,960,000 cells/cu. mm., and the leukocyte count 9,450 cells/cu. mm. The platelet count was 150,000 and 158,000 platelets/cu. mm. on repeated counts. The urinary specific gravity was 1.018; there was 1 + albuminuria, and a positive test for bile; occasional granular casts and none to two red blood cells per high power field were present in the urinary sediment. Subsequent and final urinalyses remained unchanged until the

TABLE I

Laboratory Data

Hosp. Day	Adm.	2nd	4th	6th	9th	10th*	11th	12th	14th	16th	19th	23rd	27th
Total WBC	9450	7700	12200	20300		9300	9150	9000	9300	9500	8400	8400	9200
Absolute no. atypical lymphs	2835	2695	6222	9744		2976	2745	1800	2046	1710	2100	1848	2116
Absolute no. lymphs	3780	924	2684	1624		2325	1189	1440	2046	3135	2808	3528	4600
Ceph. flocc.	3+							4+		4+	2+		3+
Serum bilirubin, direct mg./100 c.c.	1.6				5.6			2.2		0.6	0.7		0.5
Serum bilirubin, total mg./100 c.c.	3.2				11.6			5.0		1.8	1.6		1.8
Thymol turb.	8.2							8.5			4.9		4.2
BSP retention				58% in 50 min.							15% in 50 min.		
BUN	11			41	44			50	41	29			30
Direct eosin. count						282		16	28				
Serum chlorides, mEq./liter						92				106			
Serum sodium, mEq./liter						123.6				140			

* Institution of ACTH therapy.

icterus subsided with disappearance of bile in the urine, and finally an essentially negative microscopic examination with fair concentrations and only the slightest possible trace of albumin persisted. Total serum proteins were 6.4 gm. per 100 c.c., with an albumin of 3.6 gm. per 100 c.c. and a globulin of 2.8 gm. per 100 c.c. The total serum bilirubin was 3.2 mg. per 100 c.c., and the direct serum bilirubin was 1.6 mg. per 100 c.c. The cephalin flocculation was 3 + and the thymol turbidity was 8.2 units. Bromsulfalein retention was 58 per cent in 50 minutes. The prothrombin level was 87 per cent of normal. The stools were normal in appearance, but a 4 + guaiac test was present. Routine blood cultures were negative. Throat and sputum cultures revealed normal flora. The heterophil agglutination titer was 4 + at 1:256 two days after admission. Two days later it was 2 + at 1:2048, at which time the Davidson diagnostic test was 2 + at 1:640.

X-ray examination of the lungs was negative. An electrocardiogram revealed sinus tachycardia, prolonged electrical systole and incomplete right bundle branch block. Subsequent electrocardiograms revealed minor T wave changes and a return of the electrical systole to normal.

Hospital Course: The hospital course was characterized by extreme lethargy, persistent temperature elevation (figure 1), anorexia, nausea, vomiting, repeated epis-

taxis and mental confusion. The patient was given aureomycin, 500 mg. four times daily for five days. He was also given fluids, glucose and saline parenterally, but failed to improve with this therapy. In addition to his toxic appearance, he developed azotemia and increasing jaundice (table 1). There was progressive enlargement of the liver and spleen, each being palpable 7 cm. beneath the costal margins. The urinary specific gravity remained low and the urea clearance was 41 per cent of normal. Despite the administration of parenteral saline, the serum chlorides fell to 92 mEq. per liter and the sodium to 123 mEq. per liter. The serum potassium was 4.6 mEq. per liter.

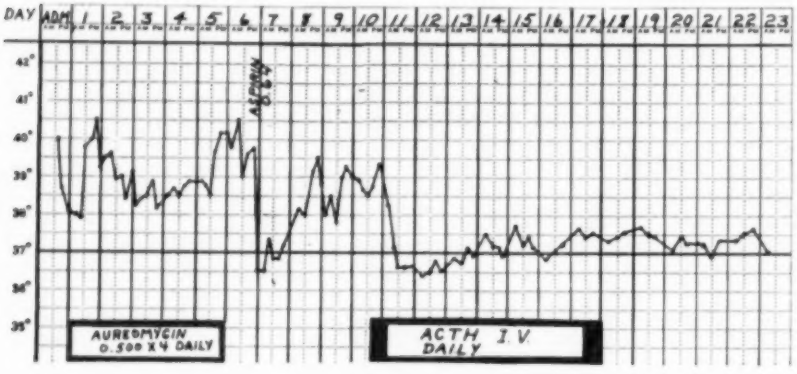


FIG. 1. Temperature chart. Note immediate reversal of febrile course within 12 hours following institution of ACTH therapy.

On the tenth hospital day he was given ACTH daily, 20 mg. (Wilson) intravenously in a slow drip over an eight hour period. Within 12 hours there was a sudden drop in temperature to normal and rapid clinical improvement, manifested by decrease in somnolence and asthenia and an increase in appetite, strength and well being. These changes were accompanied by euphoria. Objectively, within 12 hours there was visible decrease in the prominent cervical lymph nodes to one-third their former size. Subsequently, the adenopathy regressed completely and there was rapid diminution in the size of the liver and spleen to normal. The jaundice disappeared rapidly and the bromsulfalein retention fell to 15 per cent in 50 minutes.

The heterophil titer remained elevated and there was no significant change in the absolute number of atypical mononuclears. Despite the rapid return of normal values for the serum sodium and chlorides (140 and 106 mEq./liter, respectively), the urea clearance remained at 45 per cent of normal and moderate nitrogen retention persisted.

Intravenous ACTH was continued for a period of eight days. The patient was completely afebrile following the first dose of ACTH and remained afebrile thereafter. At the time of discharge he was completely asymptomatic.

DISCUSSION

The manifestations of the disease in this patient were so severe that a fatal outcome was feared. In addition to the extensive liver damage with progressive increase in jaundice, there were increasing toxicity and nitrogen retention.

There was evidence of renal and cardiac involvement, as well as moderate thrombocytopenia with epistaxis and occult blood in the stools. The temperature remained elevated and no benefit had been obtained from the use of penicillin, aureomycin and routine supportive therapy. Because of the prolonged course, the severity of the disease and the possibility of residual hepatic and renal damage, a therapeutic trial with ACTH was instituted. The clinical improvement within 12 hours of the intravenous administration of 20 mg. of ACTH was dramatic. Coincident with further ACTH therapy there was continuous and rapid clinical improvement. Although some of the improvement might be attributed to a nonspecific beneficial effect of ACTH [8, 9] (e.g., antipyretic effect, increase in appetite, sense of well being), the rapid decrease in the size of the lymph nodes and spleen indicates that ACTH may also have a specific beneficial effect. Lysis of the widespread perivascular lymphatic infiltrations following the use of ACTH might account for the reversal of the clinical course and the rapid return of liver function.

Severe asthenia is a prominent feature in most cases of infectious mononucleosis. In this patient the development of hypochloremia and hyponatremia during adequate salt intake suggests that adrenal insufficiency may have contributed to the asthenia as well as to the severity of the disease. The beneficial effect of ACTH may have been due in part to correcting adrenal insufficiency. It is possible that the low sodium and low chloride values may have been due to the renal disease.

Although the liver function improved rapidly, a significant degree of renal insufficiency persisted. Nephritis has been described in infectious mononucleosis, but renal function is said to remain unimpaired.[2, 6] The renal disease in this patient was characterized by hypertension, azotemia, persistent low specific gravity, decrease in urea clearance, slight albuminuria, and occasional red blood cells and white blood cells in the urinary sediment. Correction of the hypochloremia and hyponatremia did not improve the clearance values, and at the time of discharge low clearances and slight elevation of the blood urea nitrogen persisted. The etiology of the renal disease in this case is unknown but may have been due to the renal damage incurred during childhood.

Although the lymph nodes and spleen regressed in size rapidly following therapy with ACTH, the heterophil agglutination titer remained elevated and the absolute number of atypical mononuclear cells did not change significantly. A temporary decrease in the number of atypical cells, paralleling the decrease in lymphocytes, occurred following institution of ACTH therapy (table 1). The failure of ACTH to reverse the heterophil titer was not unexpected, in view of the observation that ACTH prevents the formation of new antibodies but has no effect on those already formed.[7]

Summary

Rapid improvement coincident with the use of ACTH occurred in a patient seriously ill with infectious mononucleosis. Further clinical trial in severe or complicated cases of infectious mononucleosis is necessary to evaluate the specificity as well as the effectiveness of ACTH in the treatment of this disease. The routine use of ACTH or cortisone in uncomplicated infectious mononucleosis is not indicated.

BIBLIOGRAPHY

1. Dolgopol, V. B., and Husson, G. S.: Infectious mononucleosis with neurologic complications, report of a fatal case, Arch. Int. Med. **83**: 179–196, 1949.
2. Wintrobe, M. M.: Clinical hematology, 1951, Lea and Febiger, Philadelphia.
3. Kaufman, R.: Infectious mononucleosis, Am. Pract. **2**: 305–308, 1951.
4. Seifert, M. H., Chandler, L. V., and Van Winkle, W. J.: Aureomycin in infectious mononucleosis, J. A. M. A. **142**: 1133–1136, 1950.
5. Burnett, B. J., and Milne, J.: Aureomycin in the treatment of infectious mononucleosis, New England J. Med. **245**: 495–496, 1951.
6. Bernstein, A.: Infectious mononucleosis, Medicine **19**: 85–159, 1940.
7. Mirick, G. S.: The effects of ACTH and cortisone on antibodies in human beings, Bull. Johns Hopkins Hosp. **88**: 332 (April) 1951.
8. Kass, E. H., and Finland, M.: Effect of ACTH on induced fever, New England J. Med. **243**: 693–695, 1950.
9. Recant, L., Ott, W. H., and Fischel, E. E.: The antipyretic effect of cortisone, Proc. Soc. Exper. Biol. and Med. **75**: 264–266, 1950.

ACUTE THYROIDITIS TREATED WITH CORTISONE*

By S. Lloyd Teitelman, M.D., and Edward F. Rosenberg, M.D., F.A.C.P.,
Chicago, Illinois

Recently we observed a patient with severe acute thyroiditis for whom usual treatment measures failed, but for whom administration of cortisone brought prompt cessation of the disease. Search of the literature revealed only one report of similar instances. Kinsell[8] gave intensive ACTH and cortisone therapy to two patients with acute thyroiditis, one of whom had severe exophthalmos. He reported prompt subsidence of acute inflammatory involvement of the gland and decrease in exophthalmos.

This case report is submitted to call further attention to this phenomenon. Additional study of this form of treatment for thyroiditis seems highly desirable in view of our experience and that of Kinsell.

Case Report

A 64 year old white salesman was admitted to Michael Reese Hospital on February 14, 1951. Three weeks prior to admission he had developed a flu-like syndrome, manifested by chilliness, fever, general aching, perspiration, cough and fatigue. He was treated by his physician with chloromycetin, after which fever and other symptoms disappeared. Five days before admission he experienced an acute attack of gout, which was quickly controlled by colchicine and rest in bed.

On February 10 he experienced a chill and fever of 103.4° F., and complained of pain in the anterior aspect of the neck, radiating to the right ear and to the occiput. The thyroid gland, particularly the isthmus and left lobe, became enlarged and tender. A diagnosis of acute thyroiditis was made, and penicillin therapy was instituted.

* Received for publication June 23, 1952.
From the Departments of Surgery and Medicine, Michael Reese Hospital and the Chicago Medical School.

The patient failed to respond to this treatment but remained febrile and was hospitalized.

Examination on admission revealed a well developed, well nourished, acutely ill white male. The temperature on admission was 103.8° F. by rectum; the pulse was 96, and respirations were 24 per minute. Physical examination disclosed no abnormalities other than enlargement, turgidity and tenderness of the thyroid gland, the left lobe being more tender than the right.

On February 15 the following laboratory results were obtained: A roentgenogram of the chest showed the lung fields to be clear, except for left hilar calcification. The cardiac contour was within normal limits. The trachea was in the midline and was not compressed. Urinalysis was negative. The level of hemoglobin was 12.8 gm. (82 per cent); red cell count, 4,390,000; white cell count, 10,000; hematocrit, 42; color index, 0.95; mean corpuscular volume, 97 microns; Wintrobe sedimentation rate, 46; plasma color, normal. The differential count was not remarkable. Blood was drawn for culture on the evening of admission, and after 48 hours showed no growth of organisms. Serum glucose was 107 mg. per cent, serum urea nitrogen, 16 mg. per cent.

Beginning on admission the patient received penicillin, 400,000 units intramuscularly twice daily, and aureomycin, 500 mg. every six hours. Warm wet dressings were applied to the neck daily for one hour. After 48 hours, the isthmus and right lobe of the thyroid gland were no longer tender, although marked tenderness of the left lobe persisted, and the patient continued to run a septic temperature.

On February 17 his course was complicated by an acute attack of gout involving the left first metatarsophalangeal joint. This was treated by local warm wet dressings, colchicine and dietary purine restrictions, and subsided in a few days. On February 18 he developed hoarseness. The dose of penicillin was cut in half, and terramycin was administered in amounts of 500 mg. every six hours. Aureomycin was discontinued after he had received a total dosage of 7.5 gm. Pain and tenderness of the thyroid gland remained unchanged. Penicillin was discontinued on February 20 after a total dosage of 4,000,000 units. The following day the dosage of terramycin was reduced to 250 mg. every six hours, and on February 23, because of continuing fever, terramycin was replaced by chloromycetin, 500 mg. every six hours, after a total dosage of 7.75 gm. All of these measures failed to influence the course of the illness.

On February 19, 21 and 23 deep x-ray therapy to the thyroid gland was administered in a dosage totaling 225 r, but following this the thyroid gland was more tender and the symptoms were more severe.

Further laboratory tests were as follows: Urinalysis on February 19 was negative, and on February 26 showed five to 10 finely granular and hyaline casts per high power field. On February 19 bacterial agglutinations for typhoid, salmonella and brucella organisms were negative. On February 21 stool examinations revealed no pathogenic bacteria or intestinal parasites. The white cell count of February 19 was 13,050, and on February 26 a complete blood count showed hemoglobin, 13.8 gm. (89 per cent); red cell count, 4,500,000; white cell count, 14,200; hematocrit, 44; color index, 0.98; mean corpuscular volume, 98 microns; sedimentation rate, 18; plasma color normal, and differential normal. After two weeks the blood culture was reported as negative for pathogens. On February 26 the heterophil antibody titer was negative. The basal metabolic rate on February 27 was plus 33.2 per cent. On the same day the following blood chemistry results were obtained: serum sodium, 134.1 mEq. per liter; serum potassium, 5.83 mEq. per liter; serum total proteins, 7.8 gm. per cent; serum true albumin, 2.3 gm. per cent; serum total globulin, 5.5 gm. per cent; serum total cholesterol, 132 mg. per cent (esterified per cent of total, 66.9).

For two weeks the patient continued to have a daily elevation of temperature,

ranging between 101° F. and 103.6° F. His symptoms remained unabated and the tenderness, enlargement and induration of the left lobe of the thyroid gland were unchanged. At no time was evidence of suppuration noted. Because of his failure to respond to antibiotic and deep roentgen therapy, it was decided to try cortisone. Accordingly, on February 27, 200 mg. of cortisone were administered intramuscularly, followed by 100 mg. on February 28 and 50 mg. on March 1. On February 28 the temperature remained normal for the first time since the onset of his illness, and pain and tenderness disappeared from the thyroid gland; there was a marked sense of general well being and an apparent increase in physical strength. The patient was discharged from the hospital on March 1 to convalesce at home.

Four days after discharge from the hospital the patient felt so well that he discontinued medications, only to note a prompt return of pain and tenderness, and a fever of 101° F. On March 7 treatment with cortisone, 100 mg. orally daily, was resumed, with repetition of the previous favorable response. The dose of cortisone was gradually reduced over a period of 12 days, during which time and subsequently the patient remained afebrile and free of symptoms. By March 29 the thyroid gland was no longer enlarged, and on April 10 the basal metabolic rate was plus 1.5 per cent. The patient seemed completely recovered. The total dosage of cortisone was 1.4 gm. He has noted no return of the symptoms to the present time.

Discussion

Cortisone and pituitary adrenocorticotropic hormone have been repeatedly observed to suppress inflammatory reactions. Therefore, it seemed reasonable to us to test its effectiveness in this patient with an inflammatory ailment resistant to the various other treatment measures employed. An adequate explanation for this effect on inflammation is not available. It has been suggested that cortisone may suppress antibody formation, augment metabolic processes active in stimulating cellular response to infection, affect peripheral vascular mechanisms controlling loss of fluid through the skin, or alter activity of heat-regulating centers in the hypothalamus.[5]

With respect to the thyroid gland, it has been shown that adrenal steroids suppress thyroid activity through pituitary inhibition (decreased secrtion of thyroid-stimulating hormone).[6]

Primary thyroiditis usually manifests itself as an inflammatory illness, either acute or chronic. Ordinarily this condition is self-limited. Investigations have disclosed no causative organism and students of this disease have generally attributed this condition to infection with a virus. The course as exemplified in our patient may be acute, accompanied by severe tenderness, high fever and marked general symptoms of malaise and aching. In some instances, however, thyroiditis runs a chronic course without fever, with only slight local pain and without other important systemic symptoms. The acute form has been observed most often in patients who are between the ages of 30 and 50. Generally this condition is associated with sore throat and pain on swallowing. Radiation of pain to the region of the ear or to the occiput is commonly reported. In the acute phase, fever ranging from 101° to 104° F. is frequently reported, and in some instances fever may continue for months. Treatment with antibiotics has generally failed to influence the course of this severe, acute type of thyroiditis.[2, 9] Symptoms of hyperthyroidism occurred in approximately 18 per cent of 33 patients observed by Crile and Rumsey.[4] Pulse rate and rate of sedimentation of erythrocytes are generally elevated. Uptake of radiactive iodine is found to be low.

Treatment measures usually recommended include bed-rest, hot or cold moist applications, iodine, thiouracil, x-ray treatments and antibiotics. Thyroidectomy has been resorted to in some severe cases.[1, 3, 9]

The erratic course of this disease has caused considerable difficulty in evaluating the effects of all types of treatments, and this is true in estimating the value of cortisone in our patient. However, the prompt response to cortisone on both occasions when it was administered strongly suggested (but did not prove) that a direct beneficial effect had been produced.

In our patient the etiologic agent was not discovered. The negative blood cultures, absence of leukocytosis, failure to respond to penicillin and history of antecedent infection of the upper respiratory tract all suggested a possible virus etiology. Since antibiotics and roentgen therapy did not shorten the course of the disease, we felt justified in employing cortisone as a nonspecific agent.

The prompt recrudescence of symptoms on cessation of cortisone suggested that the fundamental disease process was only suppressed rather than cured after the first course of cortisone. However, the clinical arrest of this disease persisted when cortisone was discontinued after the second administration, and this suggested that the course of the illness had been definitely interrupted.

Summary

A case is presented of a patient with acute thyroiditis who responded abruptly and favorably to the administration of cortisone. Other therapeutic agents failed to influence the course of this disease.

Addendum

Since this report was submitted for publication, Clark and coworkers (Clark, D. E., Nelsen, T. S. and Raiman, R. J.: Subacute nonsuppurative thyroiditis treated with cortisone, J. A. M. A. **151**: 551–552, 1953) reported three patients with subacute nonsuppurative thyroiditis successfully treated with cortisone.

BIBLIOGRAPHY

1. Cantwell, R. C.: Thiouracil in acute thyroiditis, Ann. Int. Med. **29**: 730–732 (Oct.) 1948.
2. Clute, H. M., and Smith, L. W.: Acute thyroiditis, Surg., Gynec. and Obst. **44**: 23–29 (Jan.) 1927.
3. Crile, G., Jr.: Treatment of thyroiditis, Arch. Surg. **57**: 443–449 (Oct.) 1948.
4. Crile, G., Jr., and Rumsey, E. W.: Subacute thyroiditis, J. A. M. A. **142**: 458–462 (Feb.) 1950.
5. Dougherty, T. F., and Schneebeli, G. L.: Role of cortisone in regulation of inflammation, Proc. Soc. Exper. Biol. and Med. **75**: 854–859 (Dec.) 1950.
6. Hill, S. R., Jr., Reiss, R. S., Forsham, P. H., and Thorn, G. W.: The effect of adrenocorticotropin and cortisone on thyroid function, J. Clin. Endocrinol. **10**: 1375–1400 (Nov.) 1950.
7. King, B. T., and Rosellini, L. J.: Treatment of acute thyroiditis with thiouracil, J. A. M. A. **129**: 267–268 (Sept.) 1945.
8. Kinsell, L. W.: Application of ACTH and adrenal steroid hormone, Ann. Int. Med. **35**: 615–651 (Sept.) 1951.
9. Kisner, W. H., Reganis, J., and Haughton, D.: Thyroiditis, New Orleans M. and S. J. **102**: 217–222 (Nov.) 1949.
10. Rhoads, P. S.: ACTH and cortisone in active infections (Editorial), Arch. Int. Med. **87**: 1–3 (Jan.) 1951.

THE TREATMENT OF IDIOPATHIC HEMOCHROMATOSIS BY REPEATED PHLEBOTOMY *

By THOMAS A. WARTHIN, M.D., F.A.C.P., *Boston, Massachusetts,* EDWIN W. PETERSON, M.D., *Denver, Colorado,* and JAMES H. BARR, JR., M.D., *Minneapolis, Minnesota*

IDIOPATHIC hemochromatosis is a metabolic disorder of iron metabolism, frequently familial, and probably the result of a faulty control of the ferritin absorptive mechanism in the small intestine. This excessive absorption, combined with the body's inability to excrete significant amounts of iron, results in the deposition of excessive amounts of hemosiderin in the body. Usually 25 gm. of iron, accumulating over a period of years, are necessary to produce the tissue damage which results in the clinical picture of bronzed diabetes. The disease is characteristically seen in middle aged males who present a disorder of cirrhosis, diabetes and hypogonadism, associated with clinically determinable excessive deposits of iron in the liver, skin and bone marrow, an elevated serum iron and complete saturation of the iron-carrying beta globulin of the serum. Fatal termination within one to three years after recognition has been usual, but not invariable.[1] The rare occurrence of the disease in females has been explained by the recurrent iron loss through menstruation during those decades of life which might be called the incubation period of the disorder. Finch [2] and others [3, 4] have logically suggested that frequent phlebotomy might remove these massive desposits of iron and either halt the progression of the tissue damage or perhaps even reverse some of the injury produced by its presence. In certain patients the plasma has been re-infused into the patient to prevent hypoproteinemia. We have followed a patient with this disease for four years. During the first year of observation a steady downward progression of changes occurred. In the succeeding three years, repeated phlebotomies, totaling 30 L., which removed an estimated 15 gm. of iron, were performed. The cessation of progress of the disease and improvement in the patient's condition are recorded below.

CASE REPORT

A 57 year old Veterans Administration executive was first admitted to this hospital in March, 1948. He had been retired from the Army in 1946 because of arthritis, renal calculi and fatigue. Symptoms of weakness and fatigue increased in severity. A poor appetite plus a 20 pound weight loss during the year prior to admission culminated in such a sense of exhaustion that he was unable to work and sought hospitalization.

His skin was excessively pigmented on face, arms and legs, but not elsewhere. Thoracic and axillary hair were absent. A striking gynecomastia was noted. The liver was abnormally firm and extended 4 cm. below the costal margin. The testes were small and the pubic hair was scanty.

The laboratory studies demonstrated some pyuria, a moderate normochromic anemia, hyperglobulinemia, bromsulfalein retention of 9 per cent in 45 minutes, and

* Received for publication June 28, 1952.
From the Veterans Administration Hospital, West Roxbury, Massachusetts.

a diabetic glucose tolerance curve. A skin biopsy revealed excessive amounts of hemosiderin in the outer cutis and around the sweat glands, compatible with the diagnosis of hemochromatosis.

He was given liver extract, vitamins, urinary antiseptics and testosterone rather regularly during the following year, but noted continued fatigue, weight loss and increasing pigmentation of his skin. Increasing polydipsia and polyuria occurred, and glycosuria and acetonuria appeared suddenly in May, 1949. On physical examination, an increased bronzing of the skin and a greatly enlarged liver, 7 cm. below the costal margin, were noteworthy changes from the previous hospitalization. Laboratory tests revealed a bromsulfalein retention of 12 per cent in 45 minutes, hyperglycemia and hyperglobulinemia. The 17-ketosteroids were 1.4 mg. in 24 hours.

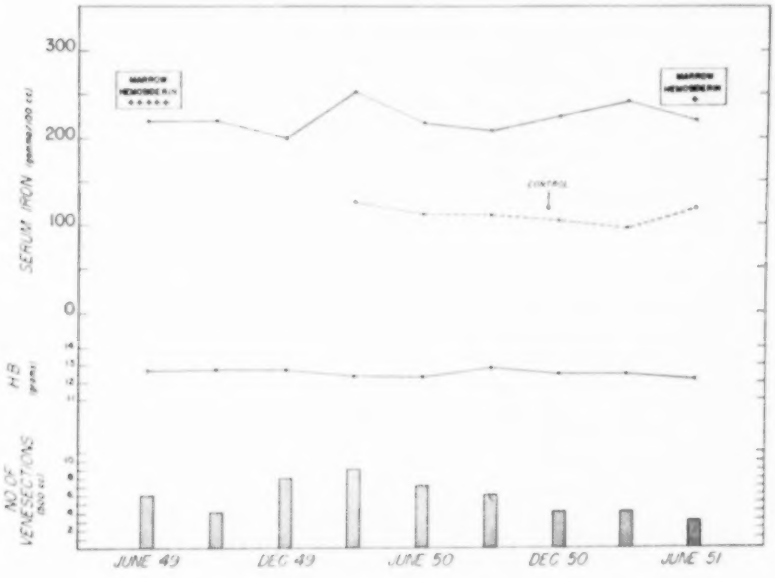


FIG. 1.

X-rays of the liver and spleen were denser than normal. Dr. Clement and Dr. Stuart Finch, of the Peter Bent Brigham Hospital, Boston, found the serum iron to be 220 gamma per 100 c.c. and the bone marrow to contain 5 plus hemosiderin. They suggested a program of repeated venesection after regulation of his diabetes, which was effected with 32 units of protamine zinc insulin and an 1,800 calorie diabetic diet.

Phlebotomies of 500 c.c. were begun on June 30, 1949, and were repeated 12 times during the next six months, 29 times during 1950, and 14 times in 1951. The patient moved to another city in September, 1951, and venesections have occurred on an average of once a month since that date. Since he was a blood type O, Rh negative donor, it was decided to use his blood in the hospital Blood Bank, and not to separate the red cells and re-infuse his plasma. The lack of effect of this removal of iron upon his serum iron and hemoglobin, but the striking decrease of marrow hemosiderin, are shown in figure 1. The saturation of his iron-binding globulin has remained at 100 per cent throughout the period of study. During the fall of

1949 an increasing hyperglobulinemia and slight anemia caused us to reduce the frequency of venesections to twice a month, but subsequent improvement enabled us to average nearly three bleedings a month throughout much of 1950. Improvement in sense of well being became apparent within six phlebotomies and he was then able to return to his sedentary duties.

Because of symptoms suggesting daily hypoglycemia he was re-admitted on June 16, 1951, for further study. He had gained 25 pounds since his last hospitalization. The skin had now lost almost all of its pigmentation, some axillary hair was present, and gynecomastia had lessened, with obvious increase in musculature. The liver could be palpated only on deep inspiration. Penile erections had recently appeared for the first time in three years. The bromsulfalein test had improved to 5 per cent retention in 45 minutes. The serum iron was 200 gamma per 100 c.c., with 100 per cent saturation of the iron-carrying globulin. The serum proteins were normal. Several bone marrow aspirations revealed marrow hemosiderin not exceeding 1 plus. Blood sugar determinations revealed that he was now becoming hypoglycemic and the dose of protamine zinc insulin was reduced to 25 units, where it has remained since. During 1952 the veins of his arms have become increasingly difficult to enter, but have been kept patent by extremely careful venesection technic and by encouraging the development of larger veins by daily exercises and by the application of simple elastic devices to elevate the venous pressure below the elbows. Liver biopsies were unfortunately never performed. At this date (June, 1952), he has continued to occupy his important administrative position with rare fatigue or glycosuria.

Discussion

The downward progress of the disorder from 1948 to 1949, followed by the striking clinical improvement during the subsequent three years of frequent venesections, seems reasonably to confirm the hopes of Finch and others that the progress of hemochromatosis could be halted by this therapy. Some improvement is undoubtedly the result of diabetic control. In this instance, actual regression of the severity of the diabetes, loss of skin pigment and return of the liver to near normal by examination and function further suggest that a portion of the pancreatic and hepatic changes are at least partially reversible and not entirely due to fibrous tissue replacement of cells. During this period of removal of approximately 15 gm. of iron from the body, the serum iron and the saturation of the iron combining globulins have remained unaltered, as might be expected. We therefore have no evidence that the characteristic fatigue or weakness of the early stages of the disease are related to these serum abnormalities. The serum iron remains as a not too difficult diagnostic test to aid in the earlier recognition of this disease. Once recognized, phlebotomy therapy can alter the formerly fatal progress of the disorder.

Summary

1. A case is presented of idiopathic hemochromatosis, treated with repeated venesection over a three year period. A striking improvement in the course of the disease followed this therapy. Early diagnosis and appropriate phlebotomy should alter the hitherto grave prognosis of the disorder.

Acknowledgment

The technical assistance of Thomas Giovanniello is gratefully acknowledged.

BIBLIOGRAPHY

1. Marble, A., and Bailey, C. C.: Hemochromatosis, Am. J. Med. **11**: 590, 1951.
2. Finch, C. A., Hegsted, M., Kinney, T. D., Thomas, E. D., Rath, C. E., Haskins, D., Finch, S., and Fluharty, R. G.: Iron metabolism, Blood **5**: 983, 1950.
3. Davis, W. D., Jr., and Arrowsmith, W. R.: The effect of repeated phlebotomies in hemochromatosis, J. Lab. and Clin. Med. **39**: 526, 1952.
4. Gitlow, S. E., and Byers, M. R.: Metabolism of iron, J. Lab. and Clin. Med. **39**: 337, 1952.

EXTRAADRENAL PHEOCHROMOCYTOMAS EXHIBITING A FALSE-NEGATIVE F 933 TEST *

By DONALD F. GIBBS,† M.B., M.R.C.P.E., and NEIL MACLEAN, M.B., Ch.B., D.P.H., M.R.C.P.E., *Edinburgh, Scotland*

THE successful surgical removal of a benign pheochromocytoma results usually in radical cure of the associated hypertension. The recognition of this condition, and its isolation from other forms of hypertension, therefore assume an importance out of proportion to its frequency.

The clinical features vary considerably. Such tumors may be associated with classic paroxysmal hypertension. Excessive sweating, palpitation, peripheral vasospastic episodes, and features suggestive of thyrotoxicosis or "anxiety states" should, in the presence of hypertension, arouse suspicion, and they are fully discussed by Smithwick.[1] Diminished carbohydrate tolerance, postural hypotension and tachycardia, unexplained pyrexia and a high metabolic rate may also be present. The diagnostic value of these observations is discussed by Graham [2] in a comprehensive review. A considerable proportion of these patients, however, present an "essential hypertension." In Graham's [2] series of 1,700 bilateral lumbodorsal splanchnicectomies, unsuspected pheochromocytomas were discovered eight times (0.47 per cent) at operation. Any reliable ancillary diagnostic aid can therefore be of considerable value in the recognition of these cases.

The pharmacologic tests devised for this purpose fall into two main groups. The first consists of administering a drug which may stimulate the tumor and thus produce a paroxysmal rise in blood pressure. Such drugs as histamine and mecholin are especially applicable to subjects with a history suggestive of paroxysmal hypertension, and with normal or only slightly raised blood pressure at the time of the test. The second group consists of drugs which can antagonize the actions of adrenalin and nor-adrenalin on the blood pressure, while failing to block the pressor action of the sympathetic system. The drug which has received most study in this group is F 933 (piperidyl-methyl-benzodioxane), and its use as a clinical test agent was first described by Goldenberg et al.[3] These workers showed that, following intravenous administration of

* Received for publication October 13, 1952.
From the Departments of Cardiology and Pathology, Royal Infirmary, Edinburgh.
† Dr. Gibbs' address, until October 1953, is: Barnes Hospital, 600 South Kingshighway, St. Louis 10, Mo.

0.25 mg./Kg. body weight, hypertension induced by infusion of adrenalin was considerably reduced. Again, Goldenberg and Aranow [4] showed that the pressor action of nor-adrenalin in man could be blocked by F 933 in the same dose. Although adrenalin has long been known to be present in excessive amounts in pheochromocytomas, only recently has nor-adrenalin been demonstrated both in the normal human adrenal medulla [5] and in the tumors.[6, 7] No other pressor agent has been demonstrated in these pheochromocytomas, and no other cause of hypertension is known to produce excess circulating adrenalin or nor-adrenalin.

A fall in blood pressure following intravenous injection of F 933 would then be expected if hypertension is due to excess of such circulating pressor amines. Similarly, no fall in blood pressure is expected if hypertension is due to any other cause; indeed, a rise in blood pressure is not uncommon, since F 933 has certain sympathomimetic properties, such as stimulation of the central nervous system.

There is considerable evidence that F 933 is of value in aiding isolation of pheochromocytomas from other causes of hypertension. The test is simple to perform and side effects were found by Goldenberg [3, 4] to be mild and transient. One of us [8] has found that only 1 per cent of 300 hypertensive subjects experienced unpleasant side effects after the use of this drug.

This paper describes a negative F 933 test in the presence of two pheochromocytomas in a subject with sustained hypertension.

Case Report

A 52 year old married woman was admitted to Dr. A. Rae Gilchrist's wards in the Royal Infirmary, Edinburgh, because of severe postorbital headaches of two years' duration. Headaches lasted up to five minutes at a time and occurred from one to eight times a day, and occasionally wakened her. They were always followed by a creeping sensation at the back of the neck and tightness around the sides and front of the neck for from five to 10 minutes. Associated with some headaches was a sensation of general trembling and purple discoloration of the left hand. There was no sweating or blanching of the hands or feet. Headaches were not associated with exertion or posture but were more likely to come during mental stress and for the two days prior to menstruation. The patient related them to a postnasal discharge of two years' duration. She had also been breathless on inclines for seven years, and complained of visual blurring for three weeks. She had been "nervous" all her life, and always preferred colder weather. There had been considerable mental stress for the five years prior to admission.

There was no renal or obstetric history of note. Her family history did not suggest vascular disease. At the age of 12 and again at the age of 31 she had been told she suffered from "rheumatic fever." Her nursing training had been interrupted at the age of 20 because of "anemia." For the last eight years she had noticed that even small amounts of alcohol made her dizzy and caused vomiting.

Examination showed a rather masculine figure, with relatively broad shoulders and narrow hips, slight facial hirsutism but normal female distribution of pubic hair. The upper eyelids were puffy and there was moderate upper lid retraction and a "thyrotoxic stare." Blood pressure was constant day by day during three weeks' observation at 220–230/130–136 mm. of Hg. It did not vary during the occasional headaches experienced in hospital, although these were in no way different from those experienced before admission. During an emotional upset the blood pressure reached

250/150 mm. of Hg but there was no headache at the time. During the sodium amytal test it fell from 240/132 mm. of Hg to 204/118 mm. of Hg; following intravenous injection of 0.3 mg. Hydergine there was no change in pressure. Cold pressor test showed a rise of 8 mm. systolic and 6 mm. diastolic. F 933 was given in a dose of 20 mg. on two occasions and the results were identical on each occasion. Figure 1 shows the response on the first occasion. The blood pressure rose from a resting level of 234/130 mm. of Hg to 258/144 mm. of Hg within two minutes and returned to the preinjection figure in 18 minutes. Postural test on a tilting table showed a resting blood pressure in the horizontal position of 226/122 mm. of Hg, which responded to a sudden swing to vertical position by a slight systolic fall in pressure, the figure four seconds after the tilt being 216/128 mm. of Hg.

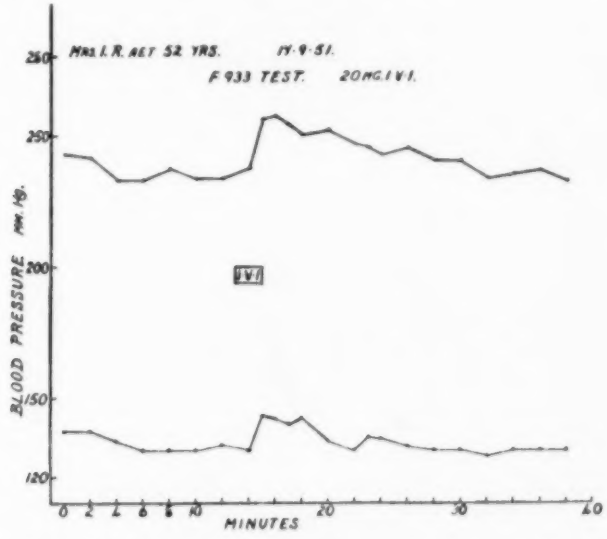


FIG. 1. Response of the blood pressure to intravenous injection of 20 mg. F 933.

The heart was slightly enlarged, with the apex beat in the fifth left interspace one-half inch outside the midclavicular line; apex impulse was heaving; the multiple unipolar lead electrocardiogram showed left ventricular hypertrophy in a horizontal heart, and there was radiologic evidence of enlargement of the left ventricular segment. The retinae showed numerous hemorrhages, hard macular exudates, narrowing of the arterioles with enhanced reflexes and arteriovenous nipping, venous congestion and slight swelling of the optic discs. This swelling progressed and was fairly well marked before death, the picture being grade 4 (Wagener and Keith grading[9]). Urine showed persistent albuminuria of 1.0 gm./L., occasional red cells and granular and hyaline casts. Renal function was poor, the urea range having a maximal concentration of 1.3 gm. per cent (specific gravity, 1.012), and minimal concentration of 0.7 gm. per cent (specific gravity, 1.008). Blood urea nitrogen was 12 mg. per cent; intravenous pyelogram showed bifid pelvis and ureters on the right side. There was no evident abnormality in the level of either kidney. Blood Wassermann was negative; hemoglobin was 92 per cent Sahli. Body weight was 123 pounds (normal weight, 157 pounds).

Following investigations, it was decided that the hypertension was renal in origin. A course of Veriloid by mouth was commenced, in a dose of 2 mg. four times daily. On the second day the patient suddenly developed neck rigidity and signs of sixth cranial nerve paralysis. Soon afterwards she presented a picture of a pontine lesion and died 10 days later. Her blood pressure remained unaltered during that period.

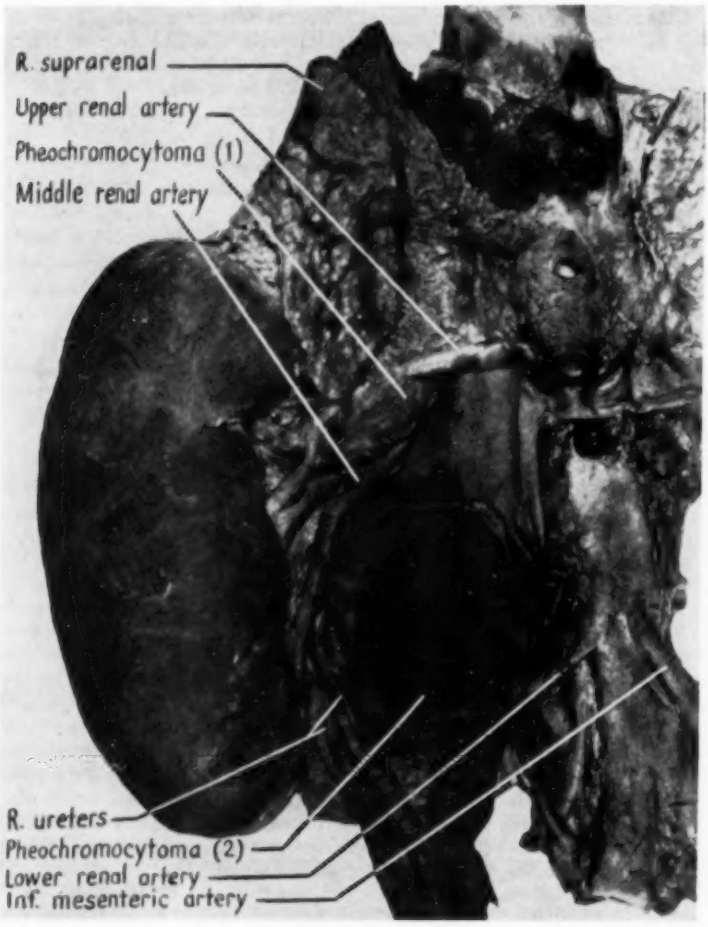


FIG. 2. The two pheochromocytomas in relation to the right kidney and three right renal arteries.

Pathologic Findings: Autopsy was performed 19 hours after death. The body was that of a middle aged woman of slim, almost masculine build, showing a slight excess of hair on the legs, upper lip and chin. The distribution of the abdominal hair and the breast development appeared normal. *The heart,* which weighed 560

gm., showed massive left ventricular hypertrophy without valvular defects. The coronary arteries were atheromatous, with segmental narrowing but without occlusion. *Brain:* A large hemorrhage present in the pons was the immediate cause of death. *The left kidney* was of normal size and shape, and was supplied by a single normal renal artery. Its capsule stripped easily to reveal a smooth congested surface; on sectioning it showed no macroscopic abnormality beyond congestion. In this it resembled the congenitally malformed *right kidney,* which was about one and one-half times normal size and possessed two pelves and two ureters. The ureters were of normal appearance, running parallel to each other and pursuing a normal course until they united 3 to 4 cm. above the bladder, which was entered by a single ureteric orifice. This kidney was supplied by three renal arteries. The upper and middle arteries arose in close apposition to one another, 1 to 1.5 cm. below the origin of the superior mesenteric artery, i.e., at approximately the normal level of origin of the right renal artery. The upper vessel ran almost transversely to enter the

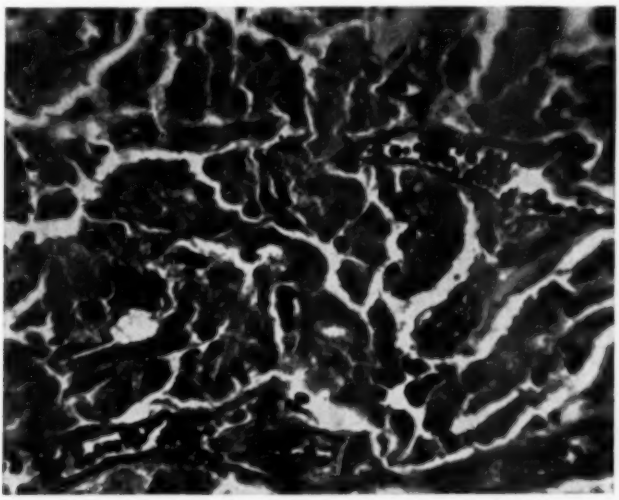


FIG. 3. Microscopic section of the larger tumor. × 425.

upper renal hilum. The middle artery ran downward and laterally to enter the lower renal hilum. The lower renal artery arose at the level of the inferior mesenteric artery, and ran at first downward and laterally and then upward and laterally to enter the lower renal hilum.

Pheochromocytomas (figure 2): (1) Situated between the upper and the middle right renal arteries there was a small encapsulated structure measuring 2 by 1 by 1.5 cm. It was composed of pale gray tissue resembling lymphoid tissue. (2) Between the middle and lower right renal arteries, lying medial to the ureters and anterolateral to the inferior vena cava, there was a tumor measuring 5.5 by 4.7 by 3.5 cm. It was encapsulated and well demarcated from the surrounding structures, and was composed of pale gray tissue with small central cysts containing thin brown fluid. On exposure to light and air, and particularly after immersion in Helly's fluid, the tumor assumed a chocolate-brown color.

The *retroperitoneal fat* was reduced in amount and showed a brown coloration most marked in the perinephric fat.

The *suprarenal glands* were normally situated; they were both slightly above average size, and the right suprarenal contained a cortical adenoma measuring approximately .5 by 1 cm. The cortical and medullary coloration was normal. The findings in the remaining organs were unexceptional and were consistent with death from hypertensive pontine hemorrhage.

Microscopic Findings: The tissues were fixed in Helly's fluid and stained with hematoxylin and eosin.

The larger tumor (figure 3) was enclosed by a capsule of relatively acellular fibrous tissue, and was composed of cells resembling the cells of the suprarenal medulla, both in appearance and in staining reaction. Large and pleomorphic cells possessed abundant cytoplasm which was often ill-defined at the margins. The round or oval nuclei contained finely divided, diffusely distributed chromatin and a nucleolus which, although quite large, was palely staining; mitoses were very infrequent. The cells were arranged in irregular masses supplied by thin-walled, well-formed blood

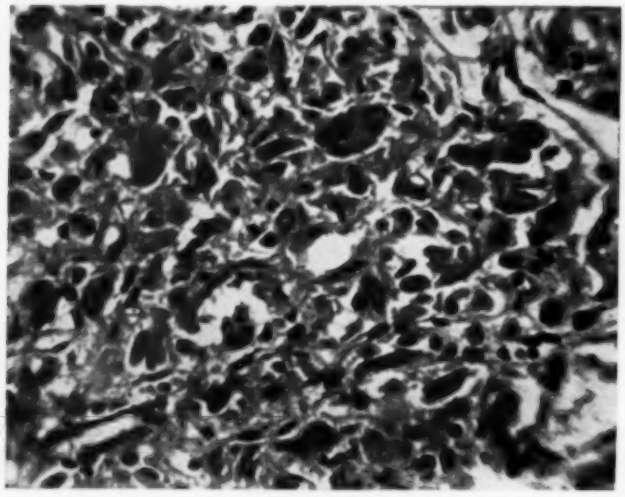


FIG. 4. Microscopic section of the smaller tumor. × 425.

vessels; there was little intercellular stroma. Rather coarse golden-brown granules were present both intracellularly and extracellularly, but were few and scattered (Prussian blue reaction, negative.) In the central areas of the tumor there were sheets of comparatively acellular fibrous tissue, devoid of chromaffin cells but containing sparse brown granules with also a negative reaction for iron. The smaller chromaffin tumor (figure 4) resembled the larger one in essential features, but its cells possessed rather less cytoplasm and showed more nuclear variation. Their appearance suggested that this tumor was growing rather more rapidly than the larger one. The cells were fairly closely packed at the periphery, but centrally, broad bands of delicate, relatively acellular, edematous, fibrous stroma intervened between columns of chromaffin cells. Brown pigment granules were, as in the larger tumor, very sparse. Neither tumor showed evidence of malignancy.

The *kidney* (figure 5) showed marked hypertensive vascular changes, with diffuse hyperplastic sclerosis of the arcuate vessels, intimal fibrosis of the interlobular

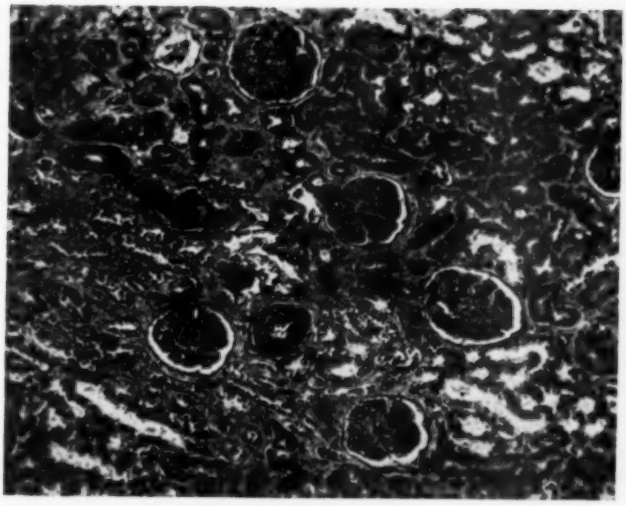


FIG. 5. Microscopic section of kidney (right). × 90.

arteries, and marked thickening and hyalinization of many of the afferent arterioles. Many of the glomeruli showed hyalinization of the capillary basement membrane, and some intercapillary fibrosis; a few were completely fibrosed, and associated with these there were some tubular atrophy and interstitial fibrosis. Although there was no frank acute arteriolar necrosis, a few vessels showed fibrinoid degeneration, and

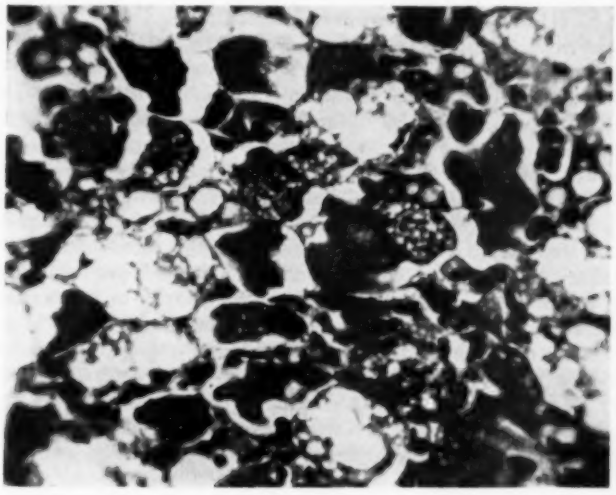


FIG. 6. Microscopic section of perinephric fat. × 400.

a few glomeruli contained fibrosed crescents. Many of the remaining organs, including muscle, showed similar hypertensive vascular change, which was particularly severe in periadrenal and pancreatic vessels.

Suprarenal: The cortex showed mild, diffuse and focal hyperplasia with good preservation of the cortical lipoid. The adenoma of the right suprarenal presented the usual appearance of a benign cortical adenoma. The medullary tissue was relatively, and possibly absolutely, reduced in amount.

The *perinephric fat* (figure 6): in some places presented the usual appearance of adipose tissue: large cells wholly occupied by lipoid, with an inconspicuous capillary network. Often, however, the tissue was highly vascular and contained fat cells varying in appearance from those filled with fat to those in which the acidophil granular cytoplasm was devoid of lipoid vacuoles. In the latter a small, round, darkly staining nucleus was situated centrally. Between these extremes were cells containing multiple small vacuoles. The capillary network was extensive, most of the cells coming into contact with dilated capillaries, sometimes on several aspects.

Chemical Findings: A portion of the larger tumor was immersed in N/10 HCl and was assayed by Dr. T. B. B. Crawford, of the Department of Pharmacology of the University of Edinburgh, with the following result:

Adrenalin content per gram of tissue—0.0205 mg.
Nor-adrenalin content per gram of tissue—1.34 mg.

Comments

Multiple extraadrenal pheochromocytomas are rare. Graham [2] traced three such cases. In addition to the present case, one of us (N. M.) has seen single pheochromocytomas lying in close apposition to each suprarenal gland. Cases with both an adrenal and an extraadrenal tumor have also been reported.[10, 3]

The association of the two extraadrenal pheochromocytomas with congenital malformation of the right kidney is interesting. The organs of Zuckerkandl, the largest extraadrenal chromaffin masses, are situated in front of the aorta at the level of origin of the inferior mesenteric artery. It seems possible that, in this case, one or both of them may have developed in an abnormal situation in association with the aberrant lower renal artery, and may later have become neoplastic. Chromaffin tissue in embryonic life, however, is widely distributed in the retroperitoneal tissues, and the relationship of the tumors to the aberrant renal artery may have been purely fortuitous.

The brown coloration of the retroperitoneal and particularly of the perinephric fat in this case, and the cellularity and vascularity on microscopic examination, were seen even more strikingly in the case of bilateral pheochromocytomas referred to above. In the latter case the mediastinal tissues were similarly affected. Graham [2] commented on the brown perinephric fat sometimes seen at operation on these tumors; the vascularity of the periadrenal tissues at operation was also noted in case 3 of Barnett et al.[11] Most wasting conditions cause depletion in the fat storage of the retroperitoneal fatty tissue which, when extreme, may result in a yellow-brown coloration of the perinephric fat. In the two cases with chromaffin tumors seen by us the patients were thin but not emaciated. The naked eye and microscopic changes in the perinephric fat, however, were more marked than is usually seen in advanced cachexia.

Consideration of experimental work [12-17] suggests that hyperadrenalinemia

might lead to excessive mobilization of fat and possibly to glycogenolysis, in the brown adipose tissues of animals. As the perinephric fat of man resembles the brown fat of animals,[18] it is possible that a similar result might follow in man. The appearance of the perinephric fat noted in some cases of pheochromocytoma may therefore represent one facet of the metabolic upset so often associated with these tumors.

A false-negative F 933 test in the presence of sustained hypertension would appear to be uncommon. A negative result in the absence of hypertension is to be expected and cannot be classed as false-negative. To our knowledge, seven instances have been recorded in which a pheochromocytoma was present and the test was clearly negative (table 1). It will be obvious, however, that without exploratory operation or autopsy false-negative tests remain undetected and consequently their true frequency is unknown. This point is perhaps insufficiently appreciated in evaluating the reliability of the F 933 test.

TABLE I

Relative Pressor Content in False-Negative Pheochromocytomas

Subject	Age (years)	Author	Adrenalin mg./gm.	Nor-adrenalin mg./gm.
P. McC.	37	Calkins et al.[21]	6.00	4.72
E. G.	28	Calkins et al.[21]	0.41	5.65
D. N.	35	Goldenberg et al.[4]	2.08	0.95
W. H.	38	Barnett et al.[11]	Not reported	
	33	Mason[22]	Not reported	
	28	Mason[23]	Not reported	
	25	Tulloh[23]	Not reported	
I. R.	52	*Present case	0.02	1.34

* Content of the large tumor

Several explanations have been suggested to account for the false-negative test. Provided the drug is active, then either the dose may be too small or else the hypertension not directly maintained at the time of the test by the pressor agents adrenalin and nor-adrenalin; that is, some secondary mechanism has been set up which is not dependent upon the continued presence of these pressor substances in the blood.

It is known that, within certain fairly broad limits, following injection of a constant dose of F 933 the greater the amount of circulating adrenalin the greater will be the fall in blood pressure. But the adrenergic blocking action of F 933 is reversible and it is possible, as suggested by Goldenberg,[4] that during a period of overwhelming secretion of the pressor agent the usual dose of F 933 would fail to lower the blood pressure. This has been shown to occur during operative handling of tumors.

Calkins et al.[19] postulate that chronic excess of circulating adrenalin may result in overproduction of adrenocorticotropic hormone by the pituitary, with resultant hyperactivity of the adrenal cortex. A degree of adrenal cortical hyperplasia was certainly present in this case.

Table 1 includes details of the relative pressor contents of the tumors where they were available. They do not suggest that preponderance of either adrenalin or nor-adrenalin is related to a false-negative test, since pheochromo-

cytomas associated with positive tests may have similar relative pressor contents.[4]

It is evident from postoperative studies that hypertension produced by pheochromocytomas may be completely alleviated following removal of the tumors. Nevertheless, in fatal cases of pheochromocytoma, arteriosclerosis was a not uncommon finding. The hypertension produced by such a tumor may therefore result in or be associated with a degree of renal arteriosclerosis, and maintenance of hypertension by secondary renal ischemia might be responsible for a false-negative test in certain instances. In this connection, case 1 of Barnett et al.[11] is instructive. In a man 38 years old, known to have been hypertensive for two years, F 933 produced a rise in blood pressure from 185/125 mm. of Hg to 225/130 mm. of Hg. A renal biopsy performed at the removal of an adrenal pheochromocytoma showed hyaline changes in many of the afferent renal arterioles and ischemic changes in a few of the glomeruli. This subject remained hypertensive, with a blood pressure of 170/122 mm. of Hg 15 months after operation.

Microscopic examination in our case revealed a degree of renal arteriosclerosis which was probably capable of sustaining hypertension, and it is suggested that this secondary renal mechanism could have accounted for the false-negative test.

No authentic false-positive result has been recorded, although in uremic subjects a positive test may apparently occur.[24, 25] In one such subject Emlet et al.[24] report a high level of circulating blood adrenalin. Calkins et al.[19] describe a case of hypertension associated with a large cell neuroblastoma in whom the F 933 test was positive. The tumor possessed no pressor activity, and no chromaffin cells could be demonstrated, but as chromaffin cells may occur in these tumors[20] the authors considered that it may have made and secreted pressor amines.

It is therefore reasonable to conclude that while a positive F 933 test result is an indication of an actively functioning pheochromocytoma, a negative test does not necessarily exclude one. There is evidence that the test is of value in detecting these tumors as causes of sustained hypertension, although the occurrence of false-negative results makes it difficult to estimate the true reliability of the test.

Summary

A case is described in which the F 933 test gave a negative result despite the presence of two extraadrenal pheochromocytomas containing excessive amounts of nor-adrenalin and adrenalin.

Possible explanations for false-negative tests are mentioned.

Acknowledgment

Our thanks are due to Dr. A. Rae Gilchrist and to Professor D. Murray Drennan for permission to publish this case and for their advice in the preparation of this paper; also to Mr. T. C. Dodds for the microphotograph production.

Addendum

(Dr. T. B. B. Crawford, Department of Pharmacology, University of Edinburgh.)

Estimation of the Adrenalin and Nor-Adrenalin Content of the Tumor: A portion of the tumor was cut into small pieces with scissors and repeatedly ground in a glass mortar

with silver sand and small quantities of 0.1 N hydrochloric acid, the acid extract being decanted off after each grinding. The combined acid extracts were freed from insoluble matter by centrifugation.

An assay of the pressor potency of the extract was carried out using the rat blood pressure preparation[26] sensitized to nor-adrenalin by the injection of hexamethonium bromide.[27, 28] Estimated in terms of nor-adrenalin, the pressor potency was found to be equivalent to 1.4 mg. nor-adrenalin per gram tumor. To find the relative proportions of adrenalin and nor-adrenalin, the two amines in aliquots of the extract were separated by paper chromatography, using the procedure described by Crawford and Outschoorn[26] with certain modifications.[28, 29] The separated amines were then eluted from the paper and estimated by a fluorometric method based on that of Lund.[30] Duplicate estimations gave values of 0.022 mg. and 0.019 mg. (mean, 0.0205 mg.) adrenalin/gm. tumor, and of 1.32 mg. and 1.36 mg. (mean, 1.34 mg.) nor-adrenalin/gm. tumor. Thus, of the total amines, 98.5 per cent was nor-adrenalin and only 1.5 per cent adrenalin.

BIBLIOGRAPHY

1. Smithwick, R. H., Green, W. E. R., Robertson, C. W., and Wilkins, R. W.: Pheochromocytoma; a discussion of symptoms, signs and procedures of diagnostic value, New England J. Med. **242**: 252, 1950.
2. Graham, J. B.: Pheochromocytoma and hypertension, Internat. Abstr. Surg. **92**: 105, 1951.
3. Goldenberg, M., Snyder, C. H., and Aranow, H.: New test for hypertension due to circulating epinephrine, J. A. M. A. **135**: 971, 1947.
4. Goldenberg, M., and Aranow, H.: Diagnosis of pheochromocytoma by the adrenergic blocking action of benzodioxane, J. A. M. A. **143**: 1139, 1950.
5. Shepherd, D. M., and West, G. B.: Nor-adrenaline and the suprarenal medulla, Brit. J. Pharmacol. **6**: 665, 1951.
6. Holton, P.: Nor-adrenaline in adrenal medullary tumors, Nature, London **163**: 217, 1949.
7. Goldenberg, M., Faber, M., Alston, E. J., and Chargaff, E. C.: Evidence for the occurrence of nor-epinephrine in the adrenal medulla, Science **109**: 534, 1949.
8. Gibbs, D. F.: Experience of F 933 a routine test in sustained hypertension, Edinburgh M. J., to be published.
9. Wagener, H. P., and Keith, N. M.: Diffuse arteriolar disease with hypertension and the associated retinal lesions, Medicine **18**: 317, 1939.
10. McCullagh, E. P., and Engel, W. J.: Pheochromocytoma with hypermetabolism, Ann. Surg. **116**: 61, 1942.
11. Barnett, A. J., Blacket, R. B., Depoorter, A. E., Sanderson, P. H., and Wilson, G. M.: The action of nor-adrenaline in man and its relation to pheochromocytoma and hypertension, Clin. Sc. **9**: 151, 1950.
12. Clément, G., and Schaeffer, G.: Démonstration de l'effet mobilisateur de l'adrénaline sur les graisses de réserve, Compt. rend. Soc. de biol. **141**: 320, 1947.
13. Wertheimer, E.: Glycogen in adipose tissue, J. Physiol. **103**: 359, 1945.
14. Renold, A. E., Marble, A., and Fawcett, D. W.: Action of insulin on deposition of glycogen and storage of fat in adipose tissue, Endocrinology **46**: 55, 1950.
15. Mirski, A.: Metabolism of adipose tissue in vitro, Biochem. J. **36**: 232, 1942.
16. Creasy, W. H., and Gray, C. H.: Enzymes concerned in the synthesis of glycogen from glucose in the brown adipose tissue, Biochem. J. **50**: 74, 1951.
17. Bell, G. H., Davidson, J. N., and Scarborough, H.: Textbook of physiology and biochemistry, 1951, E. & S. Livingstone, Ltd., Publishers, Edinburgh.
18. Selye, H., and Timiras, P.: Participation of "brown fat" tissue in the alarm reaction, Nature, London **164**: 745, 1949.
19. Calkins, E., Dana, G. W., Seed, J. C., and Howard, J. E.: On piperidylmethyl-benzodioxane (933-F), hypertension and pheochromocytoma, J. Clin. Endocrinol. **10**: 1, 1950.

20. Wahl, H. R., and Robinson, D.: Neuroblastoma of mediastinum with pheochromoblastomatous elements, Arch. Path. **35**: 571, 1943.
21. Calkins, E., Dana, G. W., and Howard, J. E.: Current methods of diagnosis of pheochromocytoma, J. A. M. A. **145**: 880, 1951.
22. Mason, R. E.: Pheochromocytoma with false negative benzodioxane tests, Am. J. Med. **11**: 524, 1951.
23. Tulloh, H. P.: Negative benzodioxane test in the presence of a pheochromocytoma, British M. J. **1**: 531, 1952.
24. Emlet, J. R., Grimson, K. S., Bell, D. M., and Orgain, E. S.: Use of piperoxane and regitine as routine tests in patients with hypertension, J. A. M. A. **146**: 1, 383, 1951.
25. Soffer, A.: False positive reaction to the piperoxane hydrochloride test for pheochromocytoma, J. A. M. A. **148**: 538, 1952.
26. Crawford, T. B. B., and Outschoorn, A. S.: The quantitative separation of adrenaline and nor-adrenaline in biological fluids and tissue extracts, Brit. J. Pharmacol. **6**: 8, 1950.
27. Outschoorn, A. S.: Unpublished personal communication to author.
28. Vogt, M.: The secretion of the denervated adrenal medulla of the cat, Brit. J. Pharmacol. **7**: 325, 1952.
29. Crawford, T. B. B.: Unpublished.
30. Lund, A.: Simultaneous fluorometric determination of adrenaline and nor-adrenaline in blood, Acta pharmacol. et toxicol. **6**: 137, 1950.

EDITORIAL

REPORT OF COMMITTEE ON CARDIAC CATHETERIZATION AND ANGIOCARDIOGRAPHY *

Introduction

Cardiac catheterization and angiocardiography are two methods which are being widely used for the investigation of acquired and congenital heart disease. Since both of these procedures entail some risk to the patient, the Scientific Council of the American Heart Association deemed it advisable to establish a committee to evaluate this risk and to recommend methods to minimize it. The constituent members of the committee were chosen on the basis of their contributions to the evolution of these methods and experience in their application.

Method of Gathering Information for This Report

Two possible methods of gathering the necessary information were suggested: (1) To submit the experiences of the individual members of the committee for analysis; (2) to obtain information from all hospitals where the procedures were being used as to the qualifications of the principal and associate investigators, the adequacy of laboratory personnel and equipment, the number of patients studied, complications, fatalities, etc. The first method was chosen because it was felt that evaluation of the experiences of a few laboratories, with a large number of patients, would more adequately reflect the possibilities and limitations of these methods than would a com-

Table I

Survey of Right Heart Catheterizations and Fatalities in Eight Medical Research Units (Complete up to January 1952)

Source of Information	Total No. of Catheterizations	No. of Deaths	Comments
University of Alabama and Johns Hopkins Hospital	1500	1	Autopsy revealed rhabdomyoma of heart.
Columbia University, Bellevue Hospital	900	1	Silicosis with tachycardia at rest; increased during severe exercise; cardiac asystole, autopsy negative.
Columbia University, Presbyterian Hospital	350	1	Mitral insufficiency; rigid catheter. Sudden pain in chest and death 2 hours after catheterization while preparing to go home. Autopsy revealed subintimal hemorrhage in infundibulum, right ventricle.
Emory University	1550	0	
Mayo Clinic	312	0	One patient died during preparation for cardiac catheterization.
Michael Reese	287	1	Not definitely attributed to procedure.
New York Hospital	192	0	
Peter Bent Brigham	600	0	

* Published at the request of the American Heart Association.

pilation of more data gathered from sources disparate in personnel, physical facilities and experience.

This report is based on the cumulative data of the members of this committee derived from approximately 5,700 right heart catheterizations in eight laboratories (table 1) and 1,325 patients studied by angiocardiography in two laboratories. It is divided into two parts: cardiac catheterization and angiocardiography.

Cardiac Catheterization

Catheters have been guided into the cardiac chambers via the venous and the arterial routes. The arterial route involves the introduction of the modified ureteral catheter against the current of flow, and includes potential injury to cardiac valves and heart, as well as injury to the vascular walls due to the force required to overcome local contraction of the arterial wall. The members of the committee are aware of individual instances of myocardial injury, torn aortic valves and introduction of the catheters into the coronary ostia resulting from this procedure. It is impossible at this time to make any specific recommendation except to urge extreme caution in the application of this experimental tool. These difficulties are much less likely to occur when the arterial catheter is not introduced into the left ventricle but is confined to the peripheral arterial system.

Subsequent remarks are confined to venous catheterization, which is established as a useful clinical tool.

Indications. The indications for venous catheterizations are difficult to establish since they will vary with the interests of the investigator. In general, the method is currently used to complete the identification of specific congenital or acquired cardiac lesions, to establish their functional significance, to trace their physiologic course, and finally to evaluate the results of surgical procedures. The method has been extended to the investigation of the physiologic functioning of other organs in health and disease, such as kidney and liver.

Contraindications. As with "Indications," it is impossible categorically to define "Contraindications." A contraindication in one laboratory may become the subject of study in another. There is no doubt that ventricular tachycardia constitutes absolute contraindication to the introduction of a cardiac catheter. Similarly, the study of patients with recent myocardial infarction and subacute bacterial endocarditis will be associated with a considerable risk of accident and patient mortality due to the primary disease itself. Certain experiences of individual committee members are germane to this problem. Thus, manifestations of rheumatic activity clinically or by ECG constitute a contraindication for immediate study by catheterization in some laboratories. Recent pulmonary embolization is considered an absolute contraindication by others. All agree that investigation of a poorly coöperative or anxious patient usually results in a poor study with incon-

clusive results, particularly in procedures which require a steady state of circulation and respiration. Finally, a critically ill patient may be expected to tolerate poorly the preparations and manipulations incident to the procedure.

Complications.

1. During cardiac catheterization.

A. *Arrhythmias:* These constitute the most common complications. Premature ventricular contractions or short bursts of ventricular tachycardia are the most frequently encountered, and are most often observed when the tip of the catheter is passing through the tricuspid valve or is located in the right ventricular cavity. Consequently, exploration of the right ventricular cavity, using the catheter as a probe, should be restricted to a minimum; lodging of the catheter there should be avoided. Premature auricular beats, auricular flutter, auricular fibrillation, nodal rhythms, and other ventricular rhythms, are seldom observed and are usually transient. Their incidence cannot always be related to any specific position of the catheter. Occasionally auricular arrhythmias have persisted for several hours after completion of the procedure, subsiding spontaneously or with the aid of specific medication (digitalis or quinidine). All of these disturbances of rhythm are more apt to occur in the presence of congenital heart disease where considerable intracardiac manipulation may be necessary to localize the defect and factors such as anoxia may contribute to myocardial irritability.

B. *Conduction Defects:* The ECG pattern of right bundle branch block is sometimes observed after the tip of the catheter has been advanced into the pulmonary artery. A shift in the position of the body of the catheter in the infundibular area may instantaneously arrest the apparent conduction disturbance. If the attack does not subside with change in the position of the catheter, the catheter should be removed.

It is important to recognize that disturbances in rhythm or conduction during cardiac catheterization may not be due to the venous catheter. Similar disturbances have been observed during introduction, and following placement of the arterial needle, with prompt subsidence following more adequate local infiltration with novocaine. Adequate anesthesia of the periarterial tissues will minimize the incidence of this complication.

C. *Syncopal Syndrome:* This syndrome is characterized by dilatation of the pupils, facial pallor, perspiration of the hands and upper lip, and yawning, associated with a bradycardia and hypotension. The investigator must always be on the alert to detect the appearance of these symptoms and either arrest the procedure, or institute measures to obviate the symptoms. They may occur at any time during the procedure or shortly after its termination. Consequently, it is important to attend the patient even after the procedure is completed.

D. *Venospasm:* This complication is not unusual. It is manifested by pain above the operative site during manipulation of the catheter, and often

subsides with cessation of manipulation. If it persists after infiltration of the site of insertion of the catheter with novocaine, the procedure should be terminated.

E. *Loops and Angulations:* These should not occur if the catheter is passed under continuous direct vision and if wide loops, especially in the auricle, are avoided. Advancement of the catheter should not be undertaken, even in the upper arm, without fluoroscopy; otherwise knots may result which are resistant to attempts at uncoiling and may require surgical removal.

F. *Trauma to Endocardium:* Traumatic lesions of the endocardium have been noted as a frequent occurrence in animals but appear to be exceedingly rare in man. Postmortem examinations have been performed within hours, days and weeks of the procedure in patients who had died of their fundamental disease, or following surgery. In nearly all instances, no evidence of cardiac injury could be detected. However, in one instance of death following cardiac catheterization, an area of sub-endocardial injury was found in the infundibulum of the right ventricle. In this instance, the lesion could probably be related to the rigidity of the probing catheter.

It cannot be overemphasized that forcing the catheter forward against resistance in any area is to be avoided. The report of instances where the catheter has been passed in the pericardial cavity, apparently by rupture through one of the cardiac veins, may be cited as emphasis on this particular point.

G. *Pyrogenic Reactions:* These complications were more frequent in the developmental days of cardiac catheterization. They may be completely avoided if proper care is exerted after catheterization to clean and rinse the catheter lumen, and if infusion sets are equipped with disposable plastic tubing rather than rubber tubing.

H. *Air Emboli:* These reactions too were more frequent during the earlier development of the method. Their consequences are more serious in the presence of congenital cardiac lesions with right to left shunt.

Miscellaneous: Specific complications may occur which are peculiar to the particular type of case under investigation. Thus, the cardiac catheter which causes no manifest obstruction or insufficiency of normal pulmonary valves may in the presence of stenosis of the pulmonary valve precipitate acute anoxia due to impaired pulmonary blood flow.

1. *Following cardiac catheterization:* Local irritation and thrombosis at the site of introduction of the venous catheter are probably related to the duration of the procedure and degree of manipulation, and are not rare. Fortunately these local thromboses have not been associated clinically with pulmonary infarction. However, pulmonary infarction has been frequently observed in the past in patients with mitral stenosis or pulmonary congestion following wedging of the catheter into a distal pulmonary artery branch for the recording of "pulmonary capillary" pressures. The complication of pulmonary infarction has been more of a problem in some laboratories than

in others. The exact cause of this apparently fine difference in the incidence of this complication is as yet unsettled. In one laboratory, this complication has been minimized by substituting autoclaving for chemical sterilization. Other investigators claim that prolonged occlusion of a terminal branch of the pulmonary artery in a congested lung bed may facilitate the occurrence of pulmonary infarction, and that, therefore, wedging should be reduced to the practical minimum and probably should not exceed 10 minutes.

2. *Fatalities:* Four deaths have occurred incident to the 5,691 catheterizations. The members of the committee are aware that other deaths have occurred in laboratories not represented in this report, but for reasons indicated above, these deaths do not lend themselves to adequate analysis. Although no attempt has been made in this report to classify the patients according to normal and various types of heart disease, it is apparent from the known interests of these laboratories that many of the patients had advanced heart disease and were particularly vulnerable to manipulative procedures of any type. This is emphasized by the death of one patient prior to introduction of the cardiac catheter while awaiting the start of the procedure. One of the three deaths that could be ascribed with certainty to the procedure revealed a rhabdomyoma of the heart at autopsy. A rigid catheter contributed to the death of another patient with subendocardial necrosis. Strenuous exercise in a patient with tachycardia at rest terminated in cardiac asystole in a third patient.

In summary, there was a mortality of less than 0.1 per cent in 5,691 cardiac catheterizations, and the possibility exists that this mortality in the light of our present knowledge and experience could have been further reduced.

3. *Prevention of serious complications:* Adequate sterilization and preparation of equipment and infusion prior to the procedure need no emphasis. During the procedure there is no better safeguard against serious complications than continuous clinical alertness and ECG observation. Any complaint of a queer or unusual feeling by the patient, a significant increase in heart rate, evidence of vagal stimulation, persistence of induced premature ventricular contractions or right bundle branch block, should lead *without delay* to termination of the procedure. Premedication with procaine amide or nembutal is considered to be of no prophylactic use. It is further suggested that transit through the right ventricle should be minimized, and pressure tracings there should be only recorded during withdrawal from the pulmonary artery. Mixed venous blood should be drawn from the pulmonary artery rather than right ventricle, except where the latter samples are essential to diagnosis. "Pulmonary capillary" pressures and samples should be obtained as rapidly as feasible.

The minor complications indicated above usually subside spontaneously following termination of the procedure. Arrhythmias which arise or persist following the termination of the procedure should be managed as any similar

spontaneous arrhythmia. The vasovagal reaction can usually be readily relieved by infiltration of the arterial site with more novocaine, oxygen inhalation and headdown position. In rare instances, it may become necessary to resort to the use of intravenous atropine for the treatment of this syndrome. Mechanical ventilators using oxygen, with facilities for delivering the gas under positive pressure, should be on hand for resuscitation. Procaine amide and quinidine are recommended for ventricular tachycardia. Digitalis glycosides, the specific ones varying with the individual preferences of the various laboratories, should be on hand to arrest paroxysms of auricular tachycardia or fibrillation, especially when they are associated with heart failure. Morphine sulfate is advocated for the management of pyrogenic reactions.

However, the dreaded complications are cardiac arrest and ventricular fibrillation. The management of these complications has been of much concern, but the recommendations are fortunately largely theoretical, because of the rarity of these complicating catastrophes. For cardiac arrest there is no prophylaxis and poor prospect of treatment; surgical intervention and direct cardiac massage are advocated by some. The prophylaxis of ventricular fibrillation is the early elimination of the ventricular arrhythmias. When ventricular fibrillation occurs, various types of therapy are available. These include chemical defibrillation by means of drugs (procaine amide, procaine, quinidine) introduced via the catheter which should be removed into the superior vena cava, and various mechanical defibrillators. Once fibrillation has been established the value of drug therapy alone is very doubtful. All methods of defibrillation are advocated with more optimism than experience.

Angiocardiography

The indications for this procedure and its limitations have been published elsewhere as isolated reports and included in a recent book. Although it is a potentially valuable diagnostic supplement in investigating anatomic alterations and defects in the heart and vascular tree, it is not an innocuous procedure and mere academic interest does not warrant its application. Diodrast is the most commonly used contrast substance, but the specific contrast medium has heretofore not influenced the frequency of undesirable reactions. At the New York Hospital 1,256 patients were studied by means of 2,197 injections. This large number is the basis for our subsequent comments. The chief complication encountered was syncope, usually regarded as a manifestation of sensitivity. This sensitivity could not be predicted on the basis of skin or eye tests with the contrast substance. Syncope occurred most frequently in patients with congenital heart disease. Premedication did not seem to avert these attacks; drugs did not seem of help in relieving them. No need could be established for the electrocardiogram in this brief procedure. It is of considerable interest that in this large group of patients

there were no deaths, whereas in a group of 6,824 patients culled from 182 centers by correspondence there were 26 deaths, predominantly children with congenital cyanotic heart disease. Nearly all received epinephrine following the onset of the reaction but prior to death. The type of death was usually ascribed to respiratory arrest during, or immediately following, injection.

It seems reasonable to indicate that angiocardiography as a supplemental tool has considerable diagnostic potentiality, and should be used only in hospitals which can procure the elaborate equipment and trained personnel essential for the maximum yield of information. It is not an office procedure and, at the present time, should be used to define lesions or disordered cardiovascular architecture about which information is necessary, but cannot be obtained by any simpler measures.

Summary and Conclusions

1. Cardiac catheterization and angiocardiography can supply, if properly applied, a considerable amount of diagnostic and physiologic information in human subjects, which is otherwise not available.

2. There is a definite risk of injury or death to the subject, which is influenced by the presence, type, and severity of heart disease. This risk can be minimized by adequate precautionary measures which can probably best be effected in large centers, utilizing specially trained medical and technical personnel.

3. It is worthy of emphasis that these methods can serve physicians best as a supplement to, rather than a substitute for, clinical and radiologic examination.

Andre Cournand, M.D., Chairman
Richard J. Bing, M.D.
Lewis Dexter, M.D.
Charles Dotter, M.D.
Louis N. Katz, M.D.
James V. Warren, M.D.
Earl Wood, M.D.

REVIEWS

X-Ray Diagnosis of Chest Diseases. By COLEMAN B. RABIN, M. D., Assistant Clinical Professor of Medicine, College of Physicians and Surgeons, Columbia University. 208 pages; 17.5 × 26 cm. Williams & Wilkins Co., Baltimore 2, Md. 1952. Price, $12.00.

This work on radiology of the chest is a very usable text and reference book. The author has combined many years of experience and study with ideas and facts gained through an extensive review of the literature to produce a book that is quite complete in this particular field.

The text is divided into four sections. Part I deals with general considerations, that is, radiographic technics including special examinations, such as bronchography, angiocardiography, laminagraphy and so forth. Anatomy of the lungs is also dealt with in this section. Many illustrations are used to bring out the points under consideration.

The remaining sections of the book include general roentgen pathology, regional roentgen pathology and the differential diagnosis of various roentgen patterns. Considerable duplication is present due to the manner of division of the book, but this feature is of advantage since it gives a review of many diseases and also additional illustrations of lesions of the same diseases that present a different pattern.

The illustrations are of excellent quality. Those in the section on bronchography leave something to be desired in that few adequately demonstrate complete visualization of the bronchial tubes. The bibliography is very complete.

C. N. D.

Electrocardiography in Practice. 3rd Ed. By ASHTON GRAYBIEL, M.D., PAUL D. WHITE, M.D., LOUISE WHEELER, A.M., and CONGER WILLIAMS, M.D. 378 pages; 20.5 × 28 cm. W. B. Saunders Company, Philadelphia. 1952. Price, $10.00.

This is the third edition of "Electrocardiography in Practice," the first having appeared in 1941 and the second in 1946. The authors have been prompted by the increasing interest and investigations in the field of electrocardiography to prepare the current edition. In the preface, it is stated that the main purpose is the production of an atlas and that the book is not intended to be a textbook.

There are nearly 300 figures which are well mounted and clearly presented. Particularly valuable are the serial records and the clinical correlations. Incorporated within the book are sections on physiologic principles, methodology, the normal electrocardiogram, disorders of rhythm and conduction, alterations due to drugs and chemicals, electrocardiographic patterns, etiologic types, and electrocardiograms for practice in interpretation. The reviewer would have preferred more emphasis on principles and the electrophysiologic basis for the various electrocardiographic abnormalities rather than the emphasis placed upon electrocardiographic "patterns." The records would probably prove even more valuable were there more adequate standards and criteria given to enable the reader to reach objective interpretations of the normal and abnormal records.

The present edition will certainly prove useful as an atlas of electrocardiography. The uniform excellence of the illustrations is certainly commendable, and the presence of unipolar extremity and multiple unipolar precordial leads will make this volume a valuable addition to the physician's library.

L. S.

Outlines of Internal Medicine. 7th Ed. Edited by CECIL J. WATSON, M.D., Head, Department of Medicine, University of Minnesota. 637 pages; 22 × 29 cm. Wm. C. Brown Company, Dubuque, Iowa. 1952. Price, $13.00.

For its size and price this book does not give adequate coverage to much of the field of internal medicine. It is an aggregate of well prepared notes on a partial cross section of medicine, economically printed in double column typewriter offset. It is divided into five parts: Part I describes infectious, pulmonary, allergic, rheumatic and collagen diseases. Part II outlines diseases of blood, and of the liver, pancreas and gastrointestinal tract. Part III deals sketchily with cardiovascular and renal disease. Part IV includes deficiency, endocrine and metabolic diseases, and discusses the handling of emotional problems. Part V is devoted to clinical chemistry and microscopy and gives details of the commoner laboratory examinations applicable to internal medicine. No space is allotted to neurological disorders.

This volume is deficient in many respects. As it has no preface, it is not easy for the unacquainted to guess its intended scope. The work is apparently compiled by members of the medical faculty of the University of Minnesota and is prepared as a monumental vade mecum for their students. There is no index and the contents pages are expanded to form a poor substitute. For a seventh edition there is an inexcusably large number of misprints and these fail to enhance one's impression of the whole.

The task of criticism is made more difficult when authors refrain from stating their purpose. Whatever the immediate design of this publication, it cannot reasonably be recommended to the outside world. Though its contents are admittedly succinct and meaty, it is unthinkable that it can compete with much more comprehensive texts of similar size and price. This work can best be summarized as a bulky and too expensive collection of useful notes and references.

H. J. L. M.

Physical Foundations of Radiology. 2nd Ed. By OTTO GLASSER, Professor of Biophysics and Head of Department of Biophysics, Cleveland Clinic Foundation, Cleveland, Ohio; EDITH H. QUIMBY, Associate Professor of Radiology (Physics), College of Physicians and Surgeons, Columbia University, New York; LAURISTON S. TAYLOR, Chief, Atomic and Radiation Physics Division, National Bureau of Standards, Washington, D. C.; and J. L. WEATHERWAX, American Oncologic Hospital and Graduate School of Medicine, University of Pennsylvania, Philadelphia. 581 pages; 13 × 19.5 cm. Paul B. Hoeber, Inc., New York. 1952. Price, $6.50.

This second edition of *Physical Foundations of Radiology* has been completely revised to incorporate the rapid advances of recent years in both theory and practical applications of radiation physics. However, the authors have still been able to obtain their basic objective of presenting an elementary non-mathematical guide to radiation physics, as applied to medicine.

Almost every chapter has been revised to clarify the subject matter and to include recent advances. Approximately 70 new or revised illustrations have been added with the intent of conveying information more clearly. Radium dosage charts and roentgen-ray depth dose tables, so well known and useful to radiologists, have been greatly expanded. Several chapters have been completely re-written and two new ones on radioactive isotopes added.

This edition represents a great improvement over the first one in conveying to the physician and student the physical principles of radiology. No other publication presents such a clear, basic non-mathematical approach to this subject. It is a book which every student or physician, who has any interest in radiology, will wish to obtain.

J. M. D.

Therapy of Dermatologic Disorders, Including a Guide to Diagnosis and a Dermatologic Pharmacopeia. By SAMUEL PECK, B.S., M.D., Dermatologist to the Mount Sinai Hospital, Associate Clinical Professor of Dermatology, Columbia University, New York; and GEORGE KLEIN, M.D., Associate Visiting Dermatologist, Morrisania City Hospital, New York Medical College. 383 pages; 15.5 × 24 cm. Lea and Febiger, Philadelphia. 1951. Price, $6.50.

In general this is an excellent compendium of "tried and true" methods of treatment and makes an excellent reference book for both the general practitioner and the specialist. Of especial interest are the chapters on physical therapeutic methods. Unnecessary wordage has been eliminated and a simple style pursued. Dr. Leifer has written an excellent chapter on the treatment of the venereal diseases.

H. M. R.

Practical Dermatology for Medical Students and General Practitioners. By GEORGE M. LEWIS, M.D., F.A.C.P., Professor of Clinical Medicine (Dermatology), Cornell University Medical College; Attending Dermatologist, The New York Hospital; Secretary, the American Board of Dermatology and Syphilology. 328 pages; 16.5 × 25.5 cm. W. B. Saunders Company, Philadelphia. 1952. Price, $7.50.

From start to finish this text is well constructed, easy to read, and contains a wealth of practical material which should prove to be of great value to the student and general practitioner. The text is complete in that it deals with the more commonly seen dermatoses and offers a brief clinical description, together with a suggestion for treatment. All unnecessary details have been eliminated. The suggestions for therapy are those which have been generally accepted by most dermatologists as satisfactory. This text is generously illustrated with excellent photographs. The author has been wise to use only black and white pictures, because the color photographs used to illustrate some of the currently used texts do not compare favorably in quality with the ones reproduced in this book. The chapter on dermatologic therapy is especially good, brief and to the point. In addition to listing a formulary for the preparations used in the treatment of skin diseases, the author has also included a formulary index. It is a pleasure to recommend this book to medical students and general practitioners.

H. M. R.

Autobiography of Dr. Robert Meyer (1864–1947). 126 pages; 26 × 17.5 cm. Henry Schuman, Inc., New York. 1949. Price, $2.50.

Writing of the late Dr. Meyer's reticence about attempting an autobiography, Dr. Emil Novak in his Memoir which introduces the book says, "I believe that I may claim credit for being at least partially responsible for Meyer's later willingness to prepare this autobiography." Dr. Novak characterizes Dr. Meyer's position during the period of German preëminence in the medical world as follows, ". . . not only through his writings but through his students he became the world's dean of gynecological pathology."

The book is dedicated, "To My Friends in the United States of America." There are no chapters as such, but the material is divided into periods of years which were successive epochs in Dr. Meyer's life; the first and last sections being entitled "The Early Years," and "The Sunset Years," respectively.

As one reads the fascinating story of this great man's life, one is impressed by the breadth of his interests which embraced such fields as pathology, music, the arts, the theatre, hiking and travel. One is also impressed with the author's zest for life,

his thoroughness, his perseverance, and his great sense of humor, evidences of which abound throughout the volume.

The author describes some of his work embracing such subjects as: adenomyosis, embryology and anomalies of the genito-urinary tract, histogenesis and classification of ovarian tumors, fetal anomalies, and ovulation and menstruation. One can understand the author's accomplishments which made him outstanding in his field by reading the following sentence, "My whole life has been dedicated to my work."

Dr. Meyer was a victim of the Nazis, and the impact of that ideology upon his life is epitomized by the following paragraph, "On the 23rd of February 1932 I was nominated Honorary Professor in the Medical Faculty of the University of Berlin, the greatest honor which the University has to bestow on a person. Some years later, I think it was 1935, Hitler was malicious enough to deprive me of that honor. I do not sleep so well since!"

The book ends with the significant sentence, "Since December 14, 1945, I have been a proud citizen of the United States of America."

Dr. Meyer's Table of Ovarian Tumors (based on histogenesis rather than morphology), and a bibliography of his works complete the volume. In the index, proper names and subjects are listed together. The book is attractively bound and the print is clear.

J. E. S.

BOOKS RECEIVED

Books received during March are acknowledged in the following section. As far as practicable those of special interest will be selected for review later, but it is not possible to discuss all of them.

Blood Cells and Plasma Proteins: Their State in Nature. Memoirs of the University Laboratory of Physical Chemistry Related to Medicine and Public Health, Harvard University. Number 2. Edited by JAMES L. TULLIS. 436 pages; 23.5 × 15.5 cm. 1953. Academic Press, Inc., New York. Price, $8.50.

Bodily Physiology in Mental and Emotional Disorders. By MARK D. ALTSCHULE, M.D., Assistant Professor of Medicine, Harvard Medical School, Boston, etc. 228 pages; 22.5 × 14.5 cm. 1953. Grune & Stratton, Inc., New York. Price, $5.75.

Building America's Health: America's Health Status, Needs and Resources. Volume 2. A Report to the President by The President's Commission on the Health Needs of the Nation. 320 pages; 26 × 20 cm. (paper-bound). 1953. For sale by the Superintendent of Documents, U. S. Government Printing Office, Washington 25, D. C. Price, $1.25.

Current Therapy, 1953: Latest Approved Methods of Treatment for the Practicing Physician. Editor: HOWARD F. CONN, M.D.; Consulting Editors: M. EDWARD DAVIS, VINCENT J. DERBES, GARFIELD G. DUNCAN, HUGH J. JEWETT, WILLIAM J. KERR, PERRIN H. LONG, H. HOUSTON MERRITT, PAUL A. O'LEARY, WALTER L. PALMER, HOBART A. REIMANN, CYRUS C. STURGIS and ROBERT H. WILLIAMS. 835 pages; 27.5 × 20.5 cm. 1953. W. B. Saunders Company, Philadelphia. Price, $11.00.

Expert Committee on Insecticides: Fourth Report. World Health Organization Technical Report Series No. 54. 98 pages; 24 × 16 cm. (paper-bound). 1952. World Health Organization, Geneva; available in U. S. A. from Columbia University Press, International Documents Service, New York. Price, 65 cents.

Group Psychotherapy: Studies in Methodology of Research and Therapy. Report of a Group Psychotherapy Research Project of the U. S. Veterans Administration. By FLORENCE B. POWDERMAKER, Ph.D., M.D., Responsible Investigator; JEROME D. FRANK, Ph.D., M.D., Principal Assistant; in collaboration with JOSEPH ABRAHAMS, M.D., ALBERT E. DREYFUS, M.D., HENRY S. MAAS, Ph.D., ROBERT MACGREGOR, M.A., JOSEPH B. MARGOLIN, M.A., HELEN T. NASH, B.A., MORRIS B. PARLOFF, M.A., DAVID ROSENTHAL, Ph.D., and EDITH VARON, M.A., M.S. 615 pages; 24 × 16 cm. 1953. Published for The Commonwealth Fund by Harvard University Press, Cambridge, Massachusetts. Price, $6.50.

Hormonal and Neurogenic Cardiovascular Disorders: Endocrine and Neuro-Endocrine Factors in Pathogenesis and Treatment. By WILHELM RAAB, M.D., F.A.C.P., F.A.C.C., F.C.C.P., Professor of Experimental Medicine and Head of Cardiovascular Research Unit, University of Vermont, etc. 722 pages; 23.5 × 15.5 cm. 1953. The Williams & Wilkins Company, Baltimore. Price, $15.00.

Klinische Fehldiagnosen. By PROF. DR. M. BÜRGER. 481 pages; 24.5 × 17.5 cm. 1953. Georg Thieme Verlag, Stuttgart; agents in U. S. A.: Grune & Stratton, Inc., New York. Price, Ganzleinen DM 58.50.

Lehrbuch der Krankheiten des Herzens und der Blutstrombahn. By PROF. DR. FRITZ LANGE. 631 pages; 24.5 × 16.5 cm. 1953. Ferdinand Enke Verlag, Stuttgart. Price, Geheftet DM 67.–; Ganzleinen DM 71.–

Malaria Terminology: Report of a Drafting Committee Appointed by the World Health Organization. World Health Organization Monograph Series No. 13. By SIR GORDON COVELL, C. I. E., M.D., Adviser on Malaria, Ministry of Health, etc.; PAUL F. RUSSELL, M.D., M.P.H., Division of Medicine and Public Health, Rockefeller Foundation, New York, N. Y., U. S. A.; and N. H. SWELLENGREBEL, D.Sc., Professor of Parasitology, University of Amsterdam, etc. 82 pages; 24 × 16 cm. (paper-bound). 1953. World Health Organization, Geneva; available in U. S. A. from Columbia University Press, International Documents Service, New York. Price, $1.00.

The Management of Abdominal Operations. Edited by RODNEY MAINGOT, F.R.C.S. 1,253 pages; 25.5 × 17 cm. 1953. The Macmillan Company, New York. Price, $24.00.

Modern Treatment: A Guide for General Practice. By 53 Authors; edited by AUSTIN SMITH, M.D., Editor of the Journal of the American Medical Association; and PAUL L. WERMER, M.D., Secretary, Committee on Research, American Medical Association. 1,146 pages; 27 × 18.5 cm. 1953. Paul B. Hoeber, Inc., Medical Book Department of Harper & Brothers, New York. Price, $20.00.

Problems of Infancy and Childhood: Transactions of the Sixth Conference, March 17 and 18, 1952, New York, N. Y. Edited by MILTON J. E. SENN, M.D., Sterling Professor of Pediatrics and Psychiatry, Yale University School of Medicine, New Haven, Connecticut. 160 pages; 23.5 × 15.5 cm. 1953. Sponsored by the Josiah Macy, Jr. Foundation, New York. Price, $2.50.

Proceedings of the Annual Meeting, Council for High Blood Pressure Research, American Heart Association, Cleveland, Ohio, May 23–24, 1952. 113 pages; 23 × 15.5 cm. (paper-bound). 1952. American Heart Association, New York. Price, $1.75.

Pulmonary Hyaline Membranes: Report of the Fifth M & R Pediatric Research Conference. Chairman: WALDO E. NELSON, M.D., Professor of Pediatrics, Temple

University School of Medicine, etc. 94 pages; 23 × 15.5 cm. (paper-bound). 1953. M & R Laboratories, Columbus, Ohio. Available to physicians on request, without cost.

Roentgen, Radium and Radioisotope Therapy. By A. J. DELARIO, M.D., Member of the American College of Radiology, etc. 371 pages; 24.5 × 15.5 cm. 1953. Lea & Febiger, Philadelphia. Price, $7.50.

Symposium on Research into the Causes of Feeblemindedness: Reprinted from the Forty-third Annual Report of the Board of Visitors of Letchworth Village for the Fiscal Year Ended March 31, 1951. 37 pages; 23 × 15.5 cm. (paper-bound). 1952. Publication of the State of New York, Department of Mental Hygiene, published by Letchworth Village. Distributed gratis.

Das Ulkus des Magens und Zwölffingerdarms: als Problem eines Schutzstoffmangels. By DR. H. RAMB. 68 pages; 24 × 17 cm. (paper-bound). 1953. Georg Thieme Verlag, Stuttgart; agents for U. S. A.: Grune & Stratton, Inc., New York. Price, Kartoniert DM 6.50.

Die Zusammenarbeit des Geburtshelfers, des Kinderarztes und des Serologen bei der Prophylaxe und Therapie der Neugeborenen-Erythroblastose. By PROF. DR. P. DAHR, Göttingen; PROF. DR. K. H. SCHÄFER, Hamburg, and PRIV.-DOZ. DR. A. STADTMÜLLER, Göttingen. 64 pages; 21 × 14.5 cm. (paper-bound). 1953. Georg Thieme Verlag, Stuttgart; available in U. S. A. from Grune & Stratton, Inc., New York. Price, Kartoniert DM 5.70.

COLLEGE NEWS NOTES

Elections to Membership in the American College of Physicians

At the Thirty-Fourth Annual Session, held in Atlantic City, N. J., April 13–17, the following candidates were elected to membership in the College (Fellows indicated in FULL CAPITALS; Associates, Lower Case):

Edmond C. Alberton.....San Francisco, Calif.
John Ernest Alexander, Jr.....Tyler, Tex.
Henry Willard Allison.....Akron, Ohio
Samuel Alpert.....New York, N. Y. (V.A.)
George Mabry Anderson.....Lake Charles, La.
William Thomas Arnold.....Houston, Tex.
Joseph Jay Arons.....San Rafael, Calif.
Robert James Atwell.....Columbus, Ohio
Legrand Joseph Audioun.....Biloxi, Miss. (V.A.)
MORRIS AXELROD.....Brooklyn, N. Y.

Kenneth Paul Bachman.....M. C., U. S. Navy
George Pratt Ballard.....River Forest, Ill. (V.A.)
Charles Miller Ballem.....Montreal, Que., Can.
Donald Burnett Barkan.....Lynn, Mass.
Earl Stephens Barker.....Philadelphia, Pa.
GEORGE LEONARD BAUM.....Coral Gables, Fla. (V.A.)
ROBERT HOUCK BECK.....Huntingdon, Pa.
Willis Lyons Bennett.....Denver, Colo.
Max Berg.....Chicago, Ill.
NATHANIEL G. BERK.....Philadelphia, Pa.
Jack Abe Bernard.....El Paso, Tex.
Carl Emery Billings.....Evanston, Ill.
Robert Montgomery Bird.....Oklahoma City, Okla.
Ronald Clare Bishop.....East Ann Arbor, Mich.
Walter Preston Bitner.....Camp Hill, Pa.
Albert Aaron Bockman.....Philadelphia, Pa.
Joseph Howard Bolotin.....Sharon, Pa.
Donald Worcester Bortz.....Greensburg, Pa.
Joseph John Bowen, Jr.....Waterbury, Conn.
Simone Brocato.....Columbus, Ga.
Samuel Walthall Budd, Jr.....Richmond, Va.
John Reed Bumgarner.....Black Mountain, N. C.

Raymond Caren.....Beverly Hills, Calif.
Miguel Alvaro Carreras, Jr.....Tucson, Ariz.
Kenneth Malcolm Carroll.....Lancaster, Pa.
Ray Llewellyn Casterline.....Medford, Ore.
CARLETON BURKE CHAPMAN.....Minneapolis, Minn.
Stephen Aristide Chavez.....Biloxi, Miss. (V.A.)
Edward Raymond Christian.....New Orleans, La. (V.A.)
Anthony Pasquale Cipriano.....New Haven, Conn.
Robert Nelson Class.....M. C., U. S. Air Force
HERBERT LEE CLAY, JR.....Louisville, Ky.
Joseph Sullivan Clutter.....Pueblo, Colo.
Lloyd Herbert Coale.....Kansas City, Kans.

JAMES ROBERT COLVERT.....Oklahoma City, Okla.
Hadley Lewis Conn, Jr.....Philadelphia, Pa.
Loyal Lee Conrad.....Oklahoma City, Okla.
Henry Ramsey Cooper.....M. C., U. S. Navy
Robert Thomas Cotton.....Topeka, Kans. (V.A.)
Branch Craige, Jr.....El Paso, Tex.
HARRY ISAAC CRAMER.....Montreal, Que., Can.
Charles Whitmarsh Crumpton.....Madison, Wis.
JAMES HAWLEY CURRENS.....Boston, Mass.

ANGELO EMIL DAGRADI.....Long Beach, Calif. (V.A.)
LINDON LEE DAVIS.....Williston Park, N. Y.
A(LONZO) RAY DAWSON.....Richmond, Va. (V.A.)
William Hope Dean.....Big Spring, Tex.
CHARLES J(OSEPH) DEERE.....Memphis, Tenn.
Clement Delit.....Flushing, N. Y.
John Winton Deming.....Alexandria, La.
DANIEL DIAMOND.....Brooklyn, N. Y.
Albert Harold Diamondstone.....Vallejo, Calif.
Herbert William Diefendorf.....Summit, N. J.
John Alexander Di Fiore.....New York, N. Y.
FRANCIS CURTIS DOHAN.....Bala-Cynwyd, Pa.
John Williams Donahoe.....Sioux Falls, S. D.
John Michael Donohue.....Kenmore, N. Y.
Irving Speiser Dribben.....Albany, N. Y.
ISADORE NATHAN DUBIN.....Washington, D. C.
Edmund Lawrence Dubois.....Beverly Hills, Calif.
Murray Dworetzky.....New York, N. Y.

Morton Henry Edelman.....New York, N. Y.
Margaret Hay Edwards.....Philadelphia, Pa.
EARL COOK ELKINS.....Rochester, Minn.
MAX ELLENBERG.....New York, N. Y.
Eugene Joseph Ellis.....Los Angeles, Calif.
Nelles John England.....London, Ont., Can.
John McCallum Evans.....Washington, D. C.
Richard Rice Evans.....Boston, Mass.

Richard Joseph Fangman.....Omaha, Nebr.
Arthur Feinfield.....North Hollywood, Calif.
DANIEL JARED FELDMAN.....New York, N. Y.
John Edmund Fenton.....Rutland Heights, Mass. (V.A.)
Marshall Jesse Fiese.....Fresno, Calif. (V.A.)
Seymour Koeppel Fineberg.....New York, N. Y.
CHARLES CAULDWELL FOOTE.....New York, N. Y.
Morris Elmer Freedland.....Long Beach, Calif.
ARTHUR MERRIMON FREEMAN, JR.....Birmingham, Ala.
Robert Westscott Frelick.....Wilmington, Del.
JACKSON HARRISON FRIEDLANDER.....Big Spring, Tex. (V.A.)
Richard Norman Frohner.....Great Falls, Mont.
Gerald Myron Frumess.....Denver, Colo.
Alfred Miller Fulton, Jr.....Billings, Mont.
John Keith Fulton.....Wichita, Kans.

JACQUES LESTER GABRILOVE.....New York, N. Y.
Adam Edward Gamon, II.....Saginaw, Mich.
SAMUEL LEON GARGILL.....Boston, Mass.
Walter Gilbert Gasner.....Mount Vernon, N. Y.
Clifford Felix Gastineau.....Rochester, Minn.
Milton Benjamin Gellman.....Philadelphia, Pa.
JOSEPH GENNIS.....Bronx, N. Y. (V.A.)
Charles Stephen Gilbert.....Chicago, Ill.
Fred Ivan Gilbert, Jr.....Honolulu, T. H.
Robert Pettibone Gilbert.....Chicago, Ill.
Leo Gitman.....Brooklyn, N. Y.
Rayburne Wyndham Goen.....Tulsa, Okla.
Albert Milton Goggans.....Fort Worth, Tex.
Harry Goldberg.....Philadelphia, Pa.
Lester Isaac Goldsmith.....Memphis, Tenn.
George Byron Gordon.....Brooklyn, N. Y.
Edward Gosfield, Jr.....Philadelphia, Pa.
PHILIP MORRIS GOTTLIEB.....Philadelphia, Pa.
Sidney Grau.....St. Petersburg, Fla.
Dell Moore Gray.....M. C., U. S. Army
James Robert Green.....Alameda, Calif. (USPHS)
Lawrence Greenman.....Pittsburgh, Pa.
LUCIEN ANTHONY GREGG.....Pittsburgh, Pa.
Milton Grossman.....Nashville, Tenn.
CHARLES MICHAEL GRUBER, JR.....Drexel Hill, Pa.
PAUL GYORGY.....Philadelphia, Pa.

William Anthony Charles Halbeisen.....Camden, N. J.
HENRY EDWARD HAMILTON.....Iowa City, Iowa
LAURA HARE.....Indianapolis, Ind.
Jean Murray Hawkes.....Memphis, Tenn.
Harold Berger Henning.....Chattanooga, Tenn.
Earl Hill.....Minneapolis, Minn.
Harold Merrill Hill.....Redlands, Calif.
Haywood Northrop Hill.....Atlanta, Ga.
Joseph Martin Hitch.....Raleigh, N. C.
JOHN HENDRICKS HODGES.....Philadelphia, Pa.
Archie Arthur Hoffman.....M. C., U. S. Air Force
Bernard Cleveland Holland.....Durham, N. C.
GEORGE HOLLANDER.....Philadelphia, Pa.
Stephen Francis Horne.....Rocky Mount, N. C.
John Thomas Hurly.....Billings, Mont.
LUCILE WEST HUTAFF.....Winston-Salem, N. C.
Robert Steele Hutcheson, Jr.....Roanoke, Va.
Albert Lewis Hyman.....New Orleans, La.

Albert Hiroshi Ishii.....Honolulu, T. H.
Demetrios Nestor Issos.....Birmingham, Ala.

ALBERT JACKSON.....Kansas City, Mo. (V.A.)
George Watson James, III.....Richmond, Va.
Otto Henry Janton, Jr.....Philadelphia, Pa.
HERBERT WILLIAM JENKINS.....Sacramento, Calif.

William Paul Jennings.....Reading, Pa.
Charles Clifford Johnson.....Boise, Idaho
Robert Leroy Johnson.....M. C., U. S. Air Force
BEN(JAMIN) CALLOWAY JONES, JR.....Alexandria, Va.

Lawrence Irwin Kaplan.....New York, N. Y.
HARRY KESSLER.....Arlington, Va. (V.A.)
Dayton Tyler Kieswetter.....East Orange, N. J.
JOHN ANTHONY KINCZEL.....Trenton, N. J.
Joseph Dill Baker King.....Baltimore, Md.
Jack Vernon Knight.....Dobbs Ferry, N. Y.
Julian Roland Borck Knutson.....Long Beach, Calif.
Herman G. Korey.....Seattle, Wash.
Maurice Daniel Krauss.....Brooklyn, N. Y.
Nathan Kreeger.....Brooklyn, N. Y.
BENJAMIN EARL KRENTZ.....New York, N. Y.
Joseph Warren Kyle.....Memphis, Tenn.

Thaddeus Dunin Labecki.....Jackson, Miss.
Paul George La Bissoniere.....Milwaukee, Wis.
Calvin Roy Lantz, Jr.....Chicago, Ill.
Paul Giere Larson.....Sacramento, Calif.
Henry Laurens, Jr.....Ada, Okla.
Sanford Hull Lawrence.....Burbank, Calif. (V.A.)
Walter Beatman Layton.....Monterey, Calif.
Sidney Israel Lechner.....New York, N. Y.
Carroll Moton Leevy.....Jersey City, N. J.
Harold John Lehmus.....Manchester, Conn.
DAVID LEHR.....Larchmont, N. Y.
Louis Lemberg.....Miami, Fla.
Leo Howard Levine.....New York, N. Y.
WILLIAM LIKOFF.....Philadelphia, Pa.
Bernard Sylvester Lipman.....Atlanta, Ga.
Lester Samuel Lipsitch.....San Francisco, Calif.
William Locke.....New Orleans, La.
Edward Wynne Lowman.....New York, N. Y.
JOHN MORGAN LYON.....Englewood, Colo.

William Benedict MacGuire, Jr.....Chattanooga, Tenn.
FLORENCE IRIS MAHONEY.....Memphis, Tenn. (V.A.)
Leslie Bernard Mann, Jr.....Los Angeles, Calif.
SYDNEY GERALD MARGOLIN.....New York, N. Y.
Frank Marion Mateer.....Pittsburgh, Pa.
EDWARD SCHUYLER McCABE.....Philadelphia, Pa.
French Howell McCain.....Detroit, Mich.
JOHN PUTNAM MERRILL.....Boston, Mass.
WILLIAM JOSEF MESSINGER.....New York, N. Y.
JOHN WRIGHT MIDDLETON.....Galveston, Tex.
Clarence Wilbur Mills.....Atlanta, Ga.
George Illarion Mishtowt.....Washington, D. C.
Reuben Alvord Moffett.....Knoxville, Ill.
FRANK CORBIN MOISTER.....Hanover, N. H.
Eugene Julius Morhous.....White Sulphur Springs, W. Va.

J(OSEPH) LLOYD MORROW.....Passaic, N. J.
Bernard Baruch Moscovich.....Vancouver, B. C., Can.
Richard Joseph Francis Murphy.....Montreal, Que., Can.
Timothy Robert Murphy.....Wauwatosa, Wis.
JACK DUANE MYERS.....Durham, N. C.
RALPH MAYER MYERSON.....Philadelphia, Pa. (V.A.)
LAMB BOLTON MYHR.....Jackson, Tenn.

Lester August Nalefski.....Chicago, Ill.
Oscar Louis Norman Nelson.....Minneapolis, Minn.

Jacob L. Oberman.....New York, N. Y.
William Austin O'Brien, Jr.....Honeoye Falls, N. Y.
KYURO OKAZAKI.....Honolulu, T. H.
Edwin Guy Olmstead.....Milwaukee, Wis.
KERMIT EDWARD OSSERMAN.....New York, N. Y.

Patrick Samuel Pasquariello.....Philadelphia, Pa.
James Fulton Patterson.....West Newton, Mass.
Homer David Peabody, Jr.....San Diego, Calif.
BENJAMIN PEARLMAN.....Chicago, Ill.
John Peter Pearson.....Oxnard, Calif.
R(UFUS) JUDSON PEARSON.....M. C., U. S. Navy
Thomas Joseph Pekin.....Washington, D. C. (V.A.)
William Francis Perry.....Winnipeg, Man., Can.
Elbert Taylor Phelps.....Washington, D. C.
KARL PICKARD.....Brooklyn, N. Y.
Samuel Pillar.....Canandaigua, N. Y. (V.A.)
Anthony Vito Pisciotta.....Milwaukee, Wis.
GERALD IRVING PITEGOFF.....Hartford, Conn.
HOWARD FREEMAN POLLEY.....Rochester, Minn.
Charles Edward Porter.....Birmingham, Ala.
Caryl Ashby Potter, Jr.....New Orleans, La.
Lorne Douglas Proctor.....Detroit, Mich.

Thomas James Quigley.....Staten Island, N. Y.

Leonard James Rabold.....Greensboro, N. C.
LEON LIONEL RACKOW.....Montrose, N. Y. (V.A.)
CHARLES ALEXANDER RAGAN, JR.....New York, N. Y.
GORDON WOODROW RALEIGH.....Evanston, Ill.
CHARLES HENRY RAMMELKAMP, JR.....Cleveland, Ohio
John Patrick Rattigan.....Boston, Mass.
Arthur Joseph Redmond.....Rochester, N. Y.
Nathan Reeves.....Augusta, Ga.
Sidney Reiff.....Brooklyn, N. Y.
Charles Sutherland Rennie.....Vancouver, B. C., Can.
Philip Lewis Rettew.....Reading, Pa.
Charles Anthony Ribaudo.....New York, N. Y.
Fred Armstrong Rice.....Minneapolis, Minn.
Abraham B. Rimmerman.....Chicago, Ill.
MILTON HERBERT ROBBINS.....New York, N. Y.
Charles Dewees Roberts.....Englewood, N. J.
George Joseph Robertson.....Waterville, Maine

DAVID EDWARD RODGER.....Regina, Sask., Can.
Charles Ernest Roh.....Hartford, Conn.
Solomon Joshua Rosenberg.....Fort Wayne, Ind. (V.A.)
Marvin Joseph Rosenburg.....Los Angeles, Calif.
James Luther D'Aumont Roth.....Philadelphia, Pa.
(RALPH) WAYNE RUNDLES.....Durham, N. C.
Joseph John Russo.....Albany, N. Y.
Joseph Murphy Ryan.....Columbus, Ohio

Kurt Sachs.....Dearborn, Mich. (V.A.)
S(AMUEL) SENIOR SACK.....Flushing, N. Y.
Martin Cyrus Sampson.....Philadelphia, Pa.
Jack Ford Sanders.....Grand Rapids, Mich.
Charles Glenn Sawyer.....Winston-Salem, N. C.
Arthur Lawrence Scherbel.....Cleveland, Ohio
Donald John Schissel.....Des Moines, Iowa
SAMUEL T. SCHLAMOWITZ.....Syracuse, N. Y.
BURTON LEWIS SCHMIER.....Detroit, Mich.
Hartwin Adolph Schulze.....M. C., U. S. Air Force
Dwight William Schuster.....Indianapolis, Ind.
Sheldon Schwartz.....Queens Village, N. Y.
Haskell Herbert Schweid.....Cleveland Heights, Ohio
Robert Schwinger.....Forest Hills, N. Y.
Sydney Segall.....Montreal, Que., Can.
Louis Warren Sennett.....Milwaukee, Wis.
NATHAN SHAPIRO.....Cincinnati, Ohio
Burton Albert Shatz.....St. Louis, Mo.
Murray Donald Shepp.....Trenton, N. J.
Philip Shulman.....Roselle, N. J.
Charles Ross Shuman.....Jenkintown, Pa.
Leo Harold Siegel.....Newark, N. J.
RAMÓN J(ULIÁN) SIFRE.....San Juan, P. R.
John Wiltshire Sigler.....Detroit, Mich.
Murray Yale Silver.....New York, N. Y.
CHARLES SILVERBERG.....St. Louis, Mo.
James MacKenzie Sinclair.....Victoria, B. C., Can.
KARL SINGER.....Chicago, Ill.
Penn Gaskell Skillern.....Cleveland, Ohio
Norman Jay Skversky.....Philadelphia, Pa.
Alvin Slipyan.....Elmhurst, N. Y.
Samuel Milton Smith, Jr.....Louisville, Ky.
Herman Sobol.....Newark, N. J.
Frank Arthur Solomon, Jr.....San Francisco, Calif.
George Edward Spencer.....Pittsburgh, Pa.
Malcolm McClain Stanley.....Brookline, Mass.
JAMES MILTON STEELE.....Jamestown, N. Y.
Lea Chapman Steeves.....Halifax, N. S., Can.
Albert Leland Steinbach.....Detroit, Mich.
Owen Kenneth Steinbach.....Fresno, Calif.
Hugh E. Stephens.....Palm Springs, Calif.
J. Edward Stern.....El Paso, Tex.
CHESTER PRATT STEVENSON.....Boise, Idaho (V.A.)
Sydney Stonehill.....Rochester, N. Y.

Jon Vidalin Straumfjord.....Astoria, Ore.
BENJAMIN HARDY SULLIVAN, JR.....M. C., U. S. Army
MARION BALDUR SULZBERGER.....New York, N. Y.

James Tatsuo Taguchi.....Dayton, Ohio (V.A.)
John Ralph Talbot.....Madison, Wis.
Perry Clement Talkington.....Dallas, Tex.
Albert Gunter Thomas.....New York, N. Y.
Walter Simeon Thompson, Jr.....Los Angeles, Calif.
James Leo Tobin.....M. C., U. S. Air Force
John Robert Tobin, Jr.....Spokane, Wash.
Henrik Odd Tonning.....St. John, N. B., Can.
GEORGE JOSEPH TRAIN.....Brooklyn, N. Y.
Jacob Barton Tuckerman.....Cleveland, Ohio (V.A.)
JAMES LYMAN TULLIS.....Brookline, Mass.

David Unterman.....Brooklyn, N. Y.

SAMUEL VAISRUB.....Winnipeg, Man., Can.
John Edwin Vander Laan.....Muskegon, Mich.
HELEN D. VAN VACTOR.....Indianapolis, Ind.
Irwin Myron Vigran.....Beverly Hills, Calif.

LEO JOSEPH WADE.....New York, N. Y.
NORMAN MELVIN WALL.....Pottsville, Pa.
Edward Stephen Wally.....New York, N. Y.
John Henry Ward, Jr.....M. C., U. S. Navy
Allan Horace Warner.....Forest Hills, N. Y.
James Vaughn Warren.....Durham, N. C.
John Samuel Watson.....Columbus, Ohio
L(OUIS) ROBERT WEISS.....Newton Highlands, Mass. (V.A.)
Thomas Edward Weiss.....New Orleans, La.
John Martin Weller.....Boston, Mass.
LOUIS GORDON WELT.....Chapel Hill, N. C.
Morton Joseph Wiener.....Detroit, Mich.
Morris Wilburne.....Beverly Hills, Calif.
GEORGE RALPH WILLIAMSON.....Pittsburgh, Pa.
Robert Granvill Williamson.....Los Angeles, Calif.
DONALD ROBERT WILSON.....Edmonton, Alta., Can.
Maurice Goss Wince.....Akron, Ohio
Nahum Jerachmeal Winer.....New York, N. Y.
A(LBERT) WALTER WISE.....Rock Island, Ill.
CHARLES PARKER WOFFORD.....Johnson City, Tenn.
STEWART GEORGE WOLF, JR.....Oklahoma City, Okla.
Robert William Woliung.....Cincinnati, Ohio
Henry Collier Wright.....Williamstown, Mass.

John Charles Gordon Young.....Montreal, Que., Can.

Harry Frederick Zinsser, Jr.....Philadelphia, Pa.
Seymour Zuckerman.....Brooklyn, N. Y.

New Life Members

It is a pleasure for the College to announce that the following Fellows have become Life Members of the American College of Physicians since the publication of the list that appeared in last month's issue of this journal:

Dr. George C. Andrews, New York, N. Y.
Dr. Herbert Berger, Staten Island, N. Y.
Dr. Florence Polk, Drexel Hill, Pa.
Dr. M. Murray Peshkin, New York, N. Y.
Dr. Louis M. Sales, Jacksonville, Fla.
Dr. Mast Wolfson, Monterey, Calif.
Dr. Louis J. Steiner, Detroit, Mich.
Dr. James H. Thompson, San Francisco, Calif.
Dr. Margaret Bell, Ann Arbor, Mich.
Dr. W. Philip Corr, Riverside, Calif.
Dr. Arthur J. Geiger, New Haven, Conn.
Dr. Frederick C. Weber, Jr., Greenwich, Conn.
Dr. M. Irving Sparks, Cleveland, Ohio

A.C.P. Hawaii Chapter

Members of the American College of Physicians in Hawaii held a dinner meeting at Honolulu on Friday, February 20. The guest of honor at the meeting was Dr. William S. Middleton, M.A.C.P., Madison, Wis. Two etchings, of which Dr. Nils P. Larsen, College Governor for Hawaii, was the artist, were presented to Dr. Middleton. The program included an informal round-table question and answer period. Dr. Middleton was also invited to address the Hawaii Heart Association.

Monthly Report on the American College of Physicians Group Insurance Plans

This report is prepared three weeks prior to the Annual Session of the College in Atlantic City and will be superseded by the official report made at that Session.

On the Health and Accident Plan, at this date approximately six hundred additional applications are required to put this plan into effect. Had all those members who indicated interest in the plan a year ago filed their applications for this insurance, it would already be in force. The period for which the plan is open will be limited and in order that College members may be included, all who have not subscribed but who want this coverage, should apply now without further delay.

During the two months that the Health and Accident Plan has been open to subscription, some members have sent to the Association Service Office local county or state plans to be compared with the one offered by the College. In every instance the College Plan has been more liberal than any plan submitted for comparison. In no instance has there been much variance in premium among the different plans available to our members. Any member who is in doubt regarding the actual provisions of any plan is encouraged to submit it to the Association Service Office, 1500 Walnut Street, Philadelphia 2, Pennsylvania, for expert advice. A complete report will be furnished promptly. Only in this way will a member be able to compare correctly the plans and to realize the advantages offered by the College Plan.

It is assured that the College Health and Accident Plan will soon be in force. Following the effective date, there will be a short time allowed for those who have

procrastinated to join. To those who do intend to subscribe sometime in the future, the recommendation is made to send application in now and to note thereon the date when the policy is to become effective. The Association Office will bill the member for the premium at that time.

On the Malpractice Plan, policies have already gone into effect, but not as many members applied for this protection as the answers to the questionnaires distributed last year would indicate. To make this plan more attractive to the underwriters, Lloyds of London, there should be at least a 50 per cent participation by College members.

From attending the various regional meetings of the College during the past several months, representatives of our Association Service Office have learned that in a few local areas the College Malpractice Plan rates are, in a few instances, higher than those that may be secured locally. This situation has been brought to the attention of the underwriters for the College, and it is hoped that we may be successful in securing a modification of the rates in such localities, securing to our members lower rates, regardless of where they may practice. The Association Service Office will appreciate receiving information from members who have been quoted lower rates than offered under the College Plan. Please furnish the quoted rates, and, if possible, a copy of the policy offered.

Members are reminded that the College Group Plan provides for an annual reduction in premium if a representative number of members subscribe and the loss ratio is good. No member is obligated to subscribe to the College insurance plans, but those that do will be helping not only themselves but other members.

Course in Postgraduate Gastroenterology

The National Gastroenterological Association announces its Fifth Annual Course in Postgraduate Gastroenterology, to be given at the Hotel Biltmore, Los Angeles, Calif., October 15, 16 and 17, 1953. Dr. Owen H. Wangensteen, Professor of Surgery of the University of Minnesota Medical School, and Dr. I. Snapper, Director of Medical Education, Cook County Hospital, Chicago, Ill., will serve as co-directors. The faculty will be selected from medical schools in and around Los Angeles.

American Board of Internal Medicine Approves Training in Rehabilitation

The American Board of Internal Medicine has approved for credit toward Board certification, one year's training in rehabilitation given by the Department of Physical Medicine and Rehabilitation of the New York University College of Medicine for residents and fellows, according to an announcement by Howard A. Rusk, M.D., F.A.C.P., Chairman of the Department. The program is offered at the Institute of Physical Medicine and Rehabilitation of the New York University-Bellevue Medical Center and at other institutions affiliated with the Medical Center.

Fellowship in Allergy

Northwestern University Medical School offers a Fellowship in Allergy designed to provide training and experience for specialization. This Fellowship is approved by the A. M. A. Council on Medical Education and Hospitals, is accredited by the American Board of Internal Medicine for credit toward the formal training requirements of the Board, and is approved for training by the Sub-Specialty Board in Allergy. An annual stipend of $2,500–$3,600 is offered. Inquiries should be addressed to Samuel M. Feinberg, M.D., F.A.C.P., Northwestern University Medical School, 303 E. Chicago Ave., Chicago 11, Ill.

Dr. J. Roscoe Miller, F.A.C.P., Chicago, and Dr. Tom D. Spies, F.A.C.P., Birmingham, Ala., were two of five American scientists awarded honorary degrees by the University of Havana, Cuba, in January. Dr. Miller is President of Northwestern University and Dr. Spies is Director of the Spies Nutrition Clinic.

At the 59th Annual Meeting of the Association of Military Surgeons of the United States, Dr. Leonard A. Scheele, F.A.C.P., Washington, D. C., Surgeon General of the U. S. Public Health Service, was elected First Vice President, and will head the organization in 1954.

Colonel Joseph F. Siler, (MC), USA, F.A.C.P., former Commandant of the Army Medical School, and Dr. Walter A. Bloedorn, F.A.C.P., Dean of George Washington University School of Medicine, have been reëlected to the Board of Directors of the Gorgas Memorial Institute of Tropical and Preventive Medicine. In addition, Dr. Bloedorn has been appointed Secretary.

Dr. Howard T. Karsner, F.A.C.P., Washington, D. C., has been reappointed to a five-year term as a member of the Scientific Advisory Board of Consultants to the Armed Forces Institute of Pathology.

Dr. Theodore J. Bauer, F.A.C.P., has been appointed Medical Officer in Charge of the Communicable Disease Center, Public Health Service, Federal Security Agency, with headquarters in Atlanta, Ga. Dr. Bauer was formerly Chief of the Public Health Service's Division of Venereal Diseases in the Bureau of State Services, Washington, D. C.

Dr. Norman Bartram Nelson (Associate) has recently been appointed Dean of the State University of Iowa College of Medicine, Iowa City. Since 1951 Dr. Nelson has been on leave of absence from the University of California School of Medicine at Los Angeles, where he was Assistant Dean, and has been Dean of the American University of Beirut in Lebanon School of Medicine.

Dr. Norman Jolliffe, F.A.C.P., New York City, was reëlected President of The National Vitamin Foundation at the annual meeting held in New York, March 4.

Dr. Ward Darley, F.A.C.P., Dean of the Medical Center and formerly Dean of the Medical School of the University of Colorado, was appointed President of the University of Colorado at the last meeting of the Board of Regents. Dr. Darley was for many years a practitioner of internal medicine, later becoming Associate Professor of Medicine, Professor, and then Dean of the Medical School of the University of Colorado. He is a Diplomate of the National Board of Medical Examiners, Fellow of the American College of Physicians, former A.C.P. Governor for Colorado, and now President of the State University.

Dr. William Dameshek, F.A.C.P., Boston, was one of the guests of the Cancer Control Commission of the Philadelphia County Medical Society on April 22 at the annual Cancer Day. He discussed "Problems in Diagnosis" in the Symposium on Blood Cancer.

Dr. Howard B. Sprague, F.A.C.P., Boston, Dr. Meyer Naide, F.A.C.P., and Dr. Thomas M. Durant, F.A.C.P., Philadelphia, were among those who made presentations

at the annual assembly of the American Academy of General Practice in St. Louis, March 23–26. Their respective topics were: "Somatic Types in General Practice." "Diagnosis, Treatment of Peripheral Vascular Diseases," and "Medical Management of Cardiac Emergencies."

Dr. William Bennett Bean, F.A.C.P., Iowa City, addressed the Academy of Medicine of Cleveland, March 20, on "Medical Manners and Morals."

Dr. George T. Harrell, Jr., F.A.C.P., Winston-Salem, N. C., delivered one of the Kellogg Lectures in Washington, D. C., March 23, on "Electrolyte Disturbances in Clinical Practice." The lectures are sponsored by the George Washington University School of Medicine.

Dr. Lester R. Dragstedt, F.A.C.P., Chicago, delivered the Samuel Gross Lecture, sponsored by the Phi chapter of Phi Delta Epsilon fraternity, in Louisville, Ky., March 23. His subject was "Recent Studies on the Physiology of Gastric Secretions and the Peptic Ulcer Problem."

At the Fourteenth Annual Meeting of The Society for Investigative Dermatology, being held in New York City, May 30–31, Dr. Hugo R. Rony, F.A.C.P., Chicago, is one of two collaborators on "Patterns of Hair Growth Cycles in the Colored Rabbit and Their Modification by Experimental Means." Dr. John H. Lamb, Jr., F.A.C.P., Oklahoma City, is co-author of "In Vitro Studies of a Group of Blocked Steroids as Antimycotic Agents." Dr. Edward P. Cawley (Associate), Charlottesville, Va., is the principal author of "Infra-red Spectroscopic Studies of Fungi," and Dr. Walter B. Shelley (Associate), Philadelphia, is among the collaborators on "Correlative Histologic and Physiologic Studies of the Normal Human Apocrine Gland." Dr. Herman Beerman, F.A.C.P., Philadelphia, Secretary-Treasurer of the Society and Chairman of the Committee on Scientific Programs, has contributed to the presentation on "Lupus Erythematosus and Polymorphous Light Eruptions. An Experimental Study on Their Possible Relationship."

Under the direction of Dr. Thomas M. Durant, F.A.C.P., and arranged by the Philadelphia County Medical Society, the Seventeenth Annual Postgraduate Institute and Convention was held in the Society's headquarters, April 28–May 1. Dr. Jerome W. Conn, F.A.C.P., Professor of Medicine, University of Michigan Medical School, Ann Arbor, was the guest speaker and discussed "Endocrine Regulation of the Blood Sugar," in addition to participating in a panel on endocrinology. Among the Philadelphians on the program were Drs. Francis C. Wood, F.A.C.P.; Perry S. MacNeal, F.A.C.P.; William A. Jeffers, F.A.C.P.; Thomas E. Machella, F.A.C.P.; Joseph T. Freeman, F.A.C.P.; Louis B. Laplace, F.A.C.P.; Edward L. Bortz, F.A.C.P., College Regent; Edward Rose, F.A.C.P.; Carl C. Fischer, F.A.C.P.; William H. Perloff (Associate); Simon S. Leopold, F.A.C.P.; David Turnoff (Associate); Charles C. Wolferth, F.A.C.P.; Joseph B. Vander Veer, F.A.C.P.; Garfield G. Duncan, F.A.C.P.; John R. Neefe (Associate); Louis A. Soloff, F.A.C.P.; Charles M. Thompson, F.A.C.P., and Harry Shay, F.A.C.P.

Lieutenant Colonel Jack C. Shrader, (MC), USAF, (Associate), Consultant in Internal Medicine, Far East Air Forces, has been an active participant in the Korean Communications Zone Medical and Dental Society, which has sponsored programs in Pusan, Taegu and Taejon. In addition to speaking on "Use and Abuse of Anti-

biotics" in these cities, Dr. Shrader also presented a paper on "The Diagnosis and Treatment of Cardiac Arrhythmias" at the Far East Air Forces Medical Seminar held at the Johnson Air Base Hospital in February.

At the Fourth Scientific Session of the New Jersey Heart Association, held in Newark, March 18, Dr. Herrman L. Blumgart, F.A.C.P., Boston, discussed "Clinical and Electrocardiographic Differential Diagnosis of Coronary Insufficiency, Coronary Failure, and Myocardial Infarction." Guest speakers from New York City included Dr. Herbert Chasis, F.A.C.P., "Evaluation of Recent Trends in Therapy of Hypertensive Disease"; Dr. A. Wilbur Duryee, F.A.C.P., "Diagnosis and Treatment of Thromboembolism"; and Dr. Clarence E. de la Chapelle, F.A.C.P., "Myocarditis."

Dr. Francis J. Braceland, F.A.C.P., Hartford, Conn., presented a paper on "Hormones and Their Influence on the Emotions" as part of the FM postgraduate radio program sponsored by the New York Academy of Medicine on March 19.

Dr. Samuel A. Levine, F.A.C.P., Boston, delivered the annual lecture sponsored by Phi Lambda Kappa fraternity at Hahnemann Medical College and Hospital of Philadelphia on March 19. His subject was "Rest in the Treatment of Heart Failure."

Dr. Thomas E. Machella, F.A.C.P., Philadelphia, discussed the medical aspects of "Management of Ulcerative Lesions of the Upper Gastrointestinal Tract" before the Academy of Medicine of Northern New Jersey on March 17.

Dr. George L. Waldbott, F.A.C.P., Detroit, is speaking on "Mechanism of Allergic Noninfectious Pneumonitis" before the Second European Congress of Allergology that is being held in Copenhagen, Denmark, May 20–23.

Dr. Walter F. Kvale, F.A.C.P., Rochester, Minn., talked on "Diagnosis of Pheochromocytoma and Use of Hexamethonium and Apresoline in Treatment of Essential Hypertension" on March 17 in Lincoln, Neb. His address was delivered at the First Lincoln-Lancaster Medical Conference, held in the Cornhusker Hotel.

At the 161st Annual Meeting of the Connecticut State Medical Society, held in Hamden, April 27–29, Dr. Irving S. Wright, F.A.C.P., New York City, College Governor for Eastern New York, presented a paper on "Anti-Coagulant Therapy." Dr. John R. Neefe (Associate), Philadelphia, discussed "Differential Diagnosis of Jaundice and Application of Liver Function Tests." Dr. Maurice B. Strauss, F.A.C.P., Framingham, Mass., talked on "Drug Treatment in the Anemias," with Dr. John C. Leonard, F.A.C.P., Hartford, College Governor for Connecticut, presiding. Dr. Elmer C. Bartels, F.A.C.P., Boston, participated in the Symposium on Thyroid Disease, using "Clinical Manifestations of Hyperthyroidism and Preparation of Patients for Thyroidectomy" as his subject.

Dr. Asher A. White, F.A.C.P., Minneapolis, was one of the guest speakers at the 57th Annual Meeting of the Sioux Valley Medical Association that met in Sioux City, Iowa, Feb. 24–26. His topics were "Allergy in General Practice" and "Fallacy in Allergy."

"Vitamin A Metabolism in Health and Disease" was the subject used by Dr. Benjamin M. Kagan, F.A.C.P., Chicago, in addressing the National Vitamin Foundation at the annual meeting in New York City on March 4.

Dr. John G. Bielawski (Associate), Detroit, discussing "The Cardiac Patient in Industry," was one of the principal speakers at the Michigan Industrial Health Day, observed March 10 in the Sheraton-Cadillac Hotel, Detroit.

Dr. Louis H. Clerf, F.A.C.P., Philadelphia, was among the guest speakers who participated in the program on otolaryngology at the annual session of the Georgia Society of Ophthalmology and Otolaryngology, which was held March 6–7 in Savannah.

Dr. John S. L. Browne, F.A.C.P., Montreal, Can., addressed the House Officers' Association of New England Center Hospital, Boston, March 13, on "Changing Aspects of Medicine." Dr. Edwin B. Astwood, F.A.C.P., and Dr. James H. Means, F.A.C.P., Boston, were the discussers.

Dr. Edward J. Stieglitz, F.A.C.P., Washington, D. C., gave a series of lectures last month at the Milledgeville (Ga.) State Hospital. His topics concerned geriatrics and were entitled "The Challenge of Longevity," "The Aging Person," and "Anticipatory Psychiatry in Maturity."

Dr. Dorothy M. Horstmann (Associate), New Haven, Conn., discussed "Epidemiology and Pathogenesis of Poliomyelitis" at a Symposium on Poliomyelitis given at the New York Academy of Medicine under the auspices of the Committee on Public Health Relations on April 2. The Symposium was the equivalent to the annual Hermann M. Biggs Memorial Lecture.

Dr. Joseph F. Ross, F.A.C.P., Boston, was one of the speakers on the annual postgraduate day program of the Memorial and Crippled Children's Hospital, Roanoke, Va., April 1. He spoke on "Contribution of Radioactive Isotopes to the Control of Disease," and participated in a panel discussion of thyroid diseases.

Dr. Cornelius P. Rhoads, F.A.C.P., New York, delivered an address on "Horizons in Cancer Research" at the dinner meeting of the annual Mid-West Cancer Conference, held in Wichita, Kan., April 2–3.

Dr. James H. Means, F.A.C.P., Boston, delivered the annual Hanau W. Loeb Lecture on "The Need for Iodine" at the St. Louis University School of Medicine, March 26. The talk was sponsored by the Alpha Pi chapter of Phi Delta Epsilon fraternity.

Four members of the College are among the guest speakers at the 103rd Annual Session of the Medical Association of Georgia, being held in Savannah, May 10–13. Dr. Louis H. Bauer, F.A.C.P., Hempstead, N. Y., President of the A. M. A., is addressing the opening meeting of the House of Delegates. Dr. Cyrus C. Sturgis, F.A.C.P., Ann Arbor, Mich., President-Elect of the College, is giving the Calhoun Lecture on "Some Recent Advances in Hematology." Dr. Lemuel C. McGee, F.A.C.P., Wilmington, College Governor for Delaware, is speaking on "Dysfunction of the

Colon" and "Operational Responsibilities of a Medical Department in Industry." Dr. Sydney Jacobs, F.A.C.P., New Orleans, is presenting papers on "What to Expect of the Photofluorogram" and "Diabetes and Tuberculosis."

Dr. Irving Innerfield (Associate), New York City, has recently been appointed Research Associate in Medicine at Mount Sinai Hospital, the appointment having been made by Dr. Alexander B. Gutman, F.A.C.P., Director of Medicine. Upon completion of the Antran Research Laboratory Building, Dr. Innerfield will be in charge of his own laboratory for the continuation of studies upon the application of enzymes in clinical medicine.

Dr. James A. Campbell (Associate), Albany, N. Y., resigned his position as Dean of the Albany Medical College on April 1. Effective June 1 he will become Chairman of the Department of Medicine, Presbyterian Hospital, Chicago.

Dr. Ralph A. Kinsella, F.A.C.P., former College Governor for Missouri, resigned this spring as Director of the Department of Internal Medicine at St. Louis University School of Medicine. Dr. Kinsella, who had headed the department for 29 years, will continue as Professor of Medicine and will remain active on the staff of St. Mary's Group of Hospitals.

Dr. Arthur R. Gaines, F.A.C.P., formerly of Fort Sam Houston, Tex., has recently been appointed Medical Director of the newly formed Pennsylvania State Tuberculosis Sanatorium in Lankenau Hospital, Philadelphia. Dr. Gaines retired from the U. S. Army Medical Corps last year with the rank of Major General, having served for 37 years.

Dr. George F. Schmitt, Jr., F.A.C.P., Miami, Fla., has recently been appointed Chief of Medicine at Mercy Hospital.

Dr. Franklin G. Ebaugh, F.A.C.P., Denver, was recently honored at a dinner given by friends, students and colleagues upon his retirement as Professor of Psychiatry at the University of Colorado School of Medicine after 28 years of service to the School. Dr. Ebaugh has also been Director of the Colorado Psychopathic Hospital and was formerly affiliated with the Phipps Clinic, the New Jersey State Hospital and State Reformatory, Trenton, the Philadelphia General Hospital and the University of Pennsylvania. During World War II he served as Neuropsychiatric Consultant to the Armed Forces and was awarded the Legion of Merit for distinguished service in the Pacific theater.

Dr. Charles S. Davidson, F.A.C.P., Boston, has recently resigned his position as Chief of Clinical Research of the National Institute of Arthritis and Metabolic Diseases to accept an appointment as Associate Professor of Medicine at Harvard Medical School.

Dr. Russell S. Boles, F.A.C.P., has been appointed Professor of Clinical Medicine in the School of Medicine of the University of Pennsylvania.

Dr. Henry Dolger, F.A.C.P., New York, has been promoted to Associate Attending Physician for Metabolic Diseases and Physician in charge of both the Diabetes Clinic and the Prenatal Diabetes Clinics at the Mount Sinai Hospital.

OBITUARIES

DR. SAMUEL S. BROWN

Dr. Samuel Skinner Brown (Associate) died December 13, 1952, at the age of 86. Born in 1866, Dr. Skinner attended the New York College of Dentistry, where he received his D.D.S. in 1887. He was never an active dentist, however, and in 1888 was granted the degree of Doctor of Medicine by the Long Island College Hospital, now the State University of New York College of Medicine at New York City, Brooklyn. He had practiced in Brooklyn for many years and at the time of his death was residing in Lynbrook, N. Y.

A former President of the Medical Society of the County of Kings, Dr. Skinner had been a member of the Courtesy Staff of the Adelphi Hospital. He became an Associate of the College in 1926 when it merged with the American Congress on Internal Medicine, which he had joined in 1924.

It is with regret that his passing is recorded at this time.

DR. RALPH T. HINTON

Dr. Ralph Thompson Hinton, F.A.C.P., of Quincy, Ill., died unexpectedly on December 19, 1952, at Atlanta, Ga., while visiting his son, Ralph T. Hinton, Jr.

Dr. Hinton was born in Payson, Ill., February 19, 1881. He took undergraduate work at Chaddock College and then became a preceptee to Dr. F. G. Walker of Quincy. He then went to the University of Illinois College of Medicine, receiving his M.D. degree in 1904. While in Medical School he joined Phi Rho Sigma Medical Fraternity and was elected to Alpha Omega Alpha Honorary Medical Fraternity. He interned for two years at Michael Reese Hospital. In 1907 he was named Assistant Superintendent of Jacksonville State Hospital, and in 1911 he moved to the position of Superintendent of Elgin State Hospital. From 1914 until 1917 he was also Superintendent of Peoria State Hospital before returning to Elgin.

In 1930, Dr. Hinton was called upon by Governor Small to draw up plans for the Manteno State Hospital. He was made Superintendent of this institution and one of its buildings was named in his honor.

In 1939, Dr. Hinton resigned from state service and opened offices in Quincy and Payson for general practice and psychiatry. For a time, he operated a weekly Psychiatric Clinic at Burlington, Iowa. Dr. Hinton was a member of the staff of Blessing and St. Mary's Hospitals. He was at one time Secretary of Adams County Medical Society and President of the Elgin Physicians' Club. He became a Fellow in the American College of Physicians in 1920 and was a member of the American Psychiatric Association.

Through the death of Dr. Hinton, the State of Illinois has lost one of her pioneers in psychiatry, and it is with much reluctance that she closes this chapter in her history.

CHARLES H. DRENCKHAHN, M.D., F.A.C.P.,
Governor for Southern Illinois

DR. GJERMUND HOYME

Dr. Gjermund Hoyme, F.A.C.P., died May 24, 1952, in Coronado, Calif. of acute myocardial infarction.

Dr. Hoyme was born in Eau Claire, Wis., on September 25, 1890. He was educated at St. Olaf College, Northfield, Minn., receiving his A.B. degree in 1914 and his M.D. degree from Northwestern University Medical School in 1918.

Dr. Hoyme spent most of his active medical career in Eau Claire, and in 1919 joined the staffs of the Luther and Sacred Heart Hospitals, where he was Internist

and Staff Physician. He also became a member of the Teaching Staff at Luther Hospital in 1920 and served as Chief of Staff in 1939. He was also a member of the staff of the Midelfart Clinic.

Dr. Hoyme, who had been a Fellow of the American College of Physicians since 1929, was a Diplomate of the American Board of Internal Medicine and a member of Nu Sigma Nu fraternity. In addition to being a member of his local and state medical societies, Dr. Hoyme was also a member of the Radiological Society of North America and the American Therapeutic Society, as well as an honorary member of the Minnesota Society of Internal Medicine.

DR. FRANCIS WILLIAM HUGHES

Dr. Francis William Hughes, F.A.C.P., who practiced for many years in London, Ontario, died on January 16, 1953, from complications following a fracture of the femur. He was born in London in 1865 and received his education in that city, graduating from the University of Western Ontario Faculty of Medicine in 1894. After an internship in Victoria Hospital, London, Ontario, he continued his postgraduate training at the London Hospital and University College Hospital in London, England, and in Germany.

Dr. Hughes then returned to London, Ontario, where he practiced until his retirement in 1949. He was a member of the active staff of Victoria Hospital for many years and its Chairman in 1937. In addition, he was a long time member of the Department of Medicine of the University of Western Ontario Faculty of Medicine, serving as Instructor and Lecturer in Medicine for some ten years before becoming Assistant Professor of Medicine in 1928, which position he held until 1941. He continued to serve as an Honorary Consultant in Medicine to Victoria Hospital until his retirement.

In 1920 Dr. Hughes became a Fellow of the American College of Physicians. In 1931 a similar honor was conferred upon him by the Royal College of Physicians of Canada. He was a member of the London Academy of Medicine, the Ontario Medical Association, and the Harvey Club of London, of which he had been President.

FRANCIS S. BRIEN, M.D., F.A.C.P.

DR. ALDIS ADELBERT JOHNSON, SR.

Dr. Aldis Adelbert Johnson, Sr., F.A.C.P., a Fellow of the College since 1931, died on October 25, 1952, of myocardial infarction and complications of a prostatectomy.

Dr. Johnson was born in Maysville, Mercer County, Pa., June 16, 1880. He received his Ph.B. at Ohio State University in 1908 and then attended Cornell University for two years. His M.D. degree was received from Western Reserve University School of Medicine in 1912.

He served as Resident in Pathology at City Hospital, Cleveland, from 1912–13; Pathologist and Bacteriologist, Jennie Edmundson Memorial Hospital, Council Bluffs, from 1923 until his death; Clinical Pathologist, Council Bluffs Clinic from 1921. Dr. Johnson was Instructor in Biology, Ohio State University, 1907–08; Demonstrator in Pathology, Western Reserve University School of Medicine, 1913; Assistant Professor of Clinical Pathology, 1913–17, and Associate in Neurology, 1920–21, at the University of Nebraska College of Medicine. He was commissioned a Lieutenant, (MC), U.S.A., and rose to the rank of Major, serving from 1917 to 1919.

Dr. Johnson served as President of the Pottawattamie Medical Society, the Iowa Clinical Society, the Iowa State Board of Medical Examiners, and the Southwestern Iowa Postgraduate Medical Group. He had also been Vice President of the Iowa State Medical Society. He was a member of the Board of Directors of the Council

Bluffs Medical Society, Omaha-Douglas County Medical Society, Sioux Valley and Missouri Valley Medical Societies, Southwestern Iowa Medical Society, Ohio State Medical Society, American Medical Association, American Society of Clinical Pathologists, and the American Heart Association. He served on the Board of Education of the Council Bluffs Public School and was a Diplomate of the American Board of Internal Medicine.

Dr. Johnson was an ardent and devoted student of medicine and pathology during all of his professional career and was an outstanding influence toward the betterment of medical standards in Iowa and Nebraska. His idealism and high ethical standards were always a positive influence in his medical community.

B. F. Wolverton, M.D., F.A.C.P.,
Governor for Iowa

DR. C. EARLE JOHNSON, JR.

Dr. Chester Earle Johnson, Jr., F.A.C.P., of Meridian, Miss., died in Tampa, Fla., on January 9, 1953, of pulmonary edema, with heart failure and diabetes mellitus as contributing causes.

Dr. Johnson was born in Headland, Ala., May 2, 1906. He attended Emory University, Birmingham Southern College, and the Medical College of Alabama, receiving his M.D. from the University of Colorado School of Medicine in 1931. Dr. Johnson interned at the Jefferson-Hillman Hospital in Birmingham, Ala., during 1931–32 and spent his residency at the Piedmont Hospital in Atlanta, Ga. From 1935 to 1937 he was affiliated with the Chambers County and Alabama State Health Departments and engaged in private practice at Lineville in 1937. Dr. Johnson became Associate Medical Officer of the Veterans Administration Hospital in North Little Rock, Ark., in 1939. From 1940 to 1943 he served as Medical Officer of the Veterans Administration Hospital in Palo Alto, Calif. During the period 1943 to 1946, Dr. Johnson again served as Medical Officer, Lieutenant Commander and later Commander, (MC), U.S.N., at the U. S. Naval Hospital, Oakland. He became Assistant Physician and Associate Medical Officer of the Bryce Hospital in Tuscaloosa, Ala., in 1946. He held the position of Superintendent of the DeJarnette State Sanatorium in Staunton, Va., from 1947 to 1950. Dr. Johnson then served as Psychiatrist in Chief of the Hoye's Sanitarium in Meridian, Miss. In 1951 he purchased the Sanitarium and continued to operate it as the Earle Johnson Sanatorium until his death.

Dr. Johnson was a past President of both the Clay and Chambers County Medical Societies in Alabama. He was also a member of the East Mississippi and Mississippi State Medical Associations. He was a Diplomate of the American Board of Psychiatry and Neurology, a Fellow of the American Psychiatric Association, and a member of the Virginia Neuropsychiatric Association. He was a member of the American Medical Association, the Alabama Academy of Neurology and Psychiatry, and of local and state societies in Virginia and Alabama. He became a Fellow of the American College of Physicians in 1950.

It is with deep and sincere regret that Dr. Johnson's many friends and colleagues record his passing at this time.

L. J. Clark, M.D., F.A.C.P.,
Governor for Mississippi

DR. MAXIM POLLAK

Dr. Maxim Pollak, F.A.C.P., who was born January 20, 1891, at Gyorsziget, Hungary, died November 20, 1952, of acute myocardial infarction at Memphis, Tenn., where he had been stationed for six months as Chief of the Tuberculosis Service of the Veterans Administration Hospital.

Before coming to this country, Dr. Pollak had received his degree of Doctor of Medicine from Magyar Királyi Pázmány Petrus Tudományegyetem Orvosi Fakultasa, Budapest, in 1914. He was Resident and Chief Resident at the Municipal Hospital and Park Sanatorium, Budapest, and had served as a First Lieutenant in the Austrian-Hungarian Army during World War I.

In 1923 Dr. Pollak became Resident Physician at the Sanatorium of the Jewish Consumptive Relief Society in Spivak, Colo., and in 1925 he was appointed Tuberculosis Specialist and Chief of Clinical Laboratory at the Veterans Administration Hospital at Fort Bayard, N. M. Two years later Dr. Pollak became Medical Director of the Sanatorium of the Jewish Consumptive Relief Society at Duarte, Calif., where he also served for two years. Appointed Medical Director and Superintendent of the Peoria (Ill.) Municipal Tuberculosis Sanitarium in 1930, Dr. Pollak held this position for eighteen years before becoming Section Chief of the Veterans Administration Hospital in Downey, Ill., in 1948. At the same time he was Tuberculosis Control Officer for the Illinois State Department of Welfare. During World War II Dr. Pollak was Chairman of Medical Advisory Board No. 39, Peoria City Section of the Selective Service System.

Dr. Pollak, who was the author of numerous articles concerning tuberculosis, was a member of the National Tuberculosis Association and the American Academy of Tuberculosis Physicians, and in 1936 he was Secretary of the Tuberculosis Section of the American Hospital Association. He was also a member of the American College of Hospital Administrators and the American Medical Association. He had been a Fellow of the American College of Physicians since 1935.

DR. MILTON H. REDISH

Milton Harris Redish, M.D., F.A.C.P., Chief of the Gastroenterology Section, Veterans Administration Hospital, Brooklyn, N. Y., died suddenly August 29, 1952.

Dr. Redish was born in New York City, November 15, 1911. He received his B.S. degree from the College of the City of New York in 1932 and his M.D degree from the New York University College of Medicine in 1936. Following his internship at Montefiore Hospital, he continued training as Resident and Fellow at the New York University Post-Graduate Medical School, Montefiore Hospital, Mt. Sinai Hospital, and the Goldwater Memorial Hospital, until December 1940, when he entered the practice of internal medicine in New York City.

He served in the Navy from May, 1945, to September, 1946, with duty on the U. S. S. Rixey, and at the Naval hospitals in St. Albans, N. Y.; Corvallis, Ore., and Mare Island, Calif.

Following discharge from the Navy, Dr. Redish received full-time appointment in the Department of Medicine and Surgery, Veterans Administration, in 1946, with assignment to the Veterans Administration Center, Bath, N. Y. He was transferred to the VA Hospital, Staten Island, in 1947, as Chief of the Gastroenterology Section. In 1950 he was transferred in the same capacity to the VA Hospital, Brooklyn, at the time of its activation.

While he was in private practice, Dr. Redish held staff appointments at Goldwater Memorial Hospital and Bellevue Hospital, and held teaching appointments at the New York University College of Medicine. He was a Diplomate of the American Board of Internal Medicine and was serving as Clinical Instructor of Medicine at the State University of New York College of Medicine at New York City, Brooklyn, at the time of his death.

He was a member of the New York Academy of Medicine, New York Academy of Science, American Medical Association, New York and American Heart Associations, American Gastro-Enterological Association, Royal Society of Tropical Medicine and Hygiene, Association of Military Surgeons, and the American Asso-

ciation for the Advancement of Science. Dr. Redish was admitted to Associateship in the American College of Physicians in 1948 and became a Fellow in 1951.

He was the author of numerous papers in the field of gastroenterology. He was an extremely able internist, an excellent administrator, a brilliant teacher, and had a well developed talent for investigative work. He was outstanding among the younger career internists in the Veterans Administration.

His loss will be very keenly felt by the veterans whom he served and by his many friends and colleagues.

J. T. Boone, M.D., F.A.C.P.,
Vice Admiral (M.C.), U. S. Navy, Retired,
Governor for the Veterans Administration

DR. ROBERT S. STARR

Dr. Robert Sythoff Starr, F.A.C.P., was born in Hartford, Conn., Dec. 5, 1873, and died in Hartford, Nov. 26, 1952. He graduated from Trinity College with an A.B. degree in 1897 and received his M.D. degree from Columbia University College of Physicians and Surgeons in 1901. While still in medical school, he received an M.A. degree from Trinity College in 1900.

He interned at the Hartford Hospital from 1902 to 1904 and thereafter served at the Hartford Hospital as Assistant and Associate Visiting Physician (1907–1922) and was Cardiologist from 1922 until 1946, at which time he became Consulting Cardiologist until his retirement in 1950. Dr. Starr also served as Consulting Cardiologist to the Hartford Municipal Hospital, the Mt. Sinai Hospital, the Hartford Institute of Living (formerly the Hartford Retreat), the Children's Village, the Newington Home and Hospital for Crippled Children, the Manchester Memorial Hospital, the New Britain General Hospital, the Windham County Memorial Hospital and the Litchfield Hospital.

He was a member of the Hartford Medical Society, of which he was President in 1934, the Hartford County Medical Association, the Connecticut Medical Society and the American Medical Association. He was a member of the American Heart Association and the New England Heart Association. He was a member of the Board of Directors of the Hartford Heart Association He had been a Fellow of the American College of Physicians since 1935, was certified by the American Board of Internal Medicine in 1937 and in Cardiovascular Disease in 1941.

During World War I he served in the Army as a Captain in the Medical Corps from April 16, 1918, to January 10, 1919. During this time he was an instructor in cardiovascular disease and a special cardiovascular examiner.

Dr. Starr was an extremely able and energetic cardiologist. He was one of the pioneers in the separation of his specialty from the general practice of medicine. He was quiet by nature, calm and deliberate in habit, and invariably inspired confidence in his patients and his colleagues alike. He loved his family, his friends, his books and his summers in the quiet hills of New Hampshire. His life was a full and worthwhile one, and he leaves a myriad of friends who grieve because of his passing.

John C. Leonard, M.D., F.A.C.P.,
Governor for Connecticut

DR. NELSON W. STROHM

Dr. Nelson Wilbert Strohm, F.A.C.P., of Buffalo, N. Y., died October 22, 1952, from coronary occlusion. He was born in Sharpsburg, Pa., on December 23, 1887, and graduated from the University of Buffalo School of Medicine in 1912.

Dr. Strohm practiced in Buffalo and was considered an authority on Diseases of the Chest. He was Consultant in Tuberculosis at the J. N. Adam Memorial

Hospital, Perrysburg, in 1928, Entrance Examiner for the Ray Brook State Tuberculosis Hospital in 1922, Chest Specialist at the Veterans Administration Hospital in Batavia in 1924, Diagnostician for Tuberculosis in the Department of Health for the County of Erie and in charge of the Tuberculosis Diagnostic Clinic for the city of Lackawanna from 1919 to 1934. He served on Advisory Board No. 48, New York Selective Service, and was a member of the Saratoga Spa Authority. He was Associate Physician at the Buffalo General Hospital and Consulting Physician at the Edward J. Meyer Memorial Hospital.

Dr. Strohm served as President of the New York State Chapter of the American College of Chest Physicians in 1941 and was also President of the Erie County Medical Society that same year. He had been Vice President of the American College of Chest Physicians in 1934. He was a member of the New York State Medical Society, American Medical Association, American Public Health Association, American Academy of Tuberculosis Physicians and the American Trudeau Society. He had been a Fellow of the American College of Physicians since 1940.

Dr. Strohm was highly respected in Buffalo by both his colleagues and his patients.

EDWARD C. REIFENSTEIN, SR., M.D., F.A.C.P.,
Governor for Western New York

BRIGADIER GENERAL WILLIAM L. SHEEP

Brigadier General William Lloyd Sheep, (MC), USA, (Retired), F.A.C.P., died in Walter Reed Army Hospital on December 6, 1952, following an operation.

General Sheep was born on October 24, 1881, at Elizabeth City, N. C. Upon completion of undergraduate work at the University of North Carolina in 1904, he matriculated at George Washington University School of Medicine, Washington, D. C., where in 1906 he received the degree of Doctor of Medicine. Remaining in Washington after his graduation, he spent a year as interne in Emergency Hospital and two years as Junior Assistant Physician at St. Elizabeths Hospital.

General Sheep began his military career in 1909 when he enlisted as an officer in the Medical Reserve Corps. The following year, having completed studies in the Army Medical School, he was commissioned First Lieutenant in the Medical Corps, U. S. (Regular) Army.

During his early years in the Army, General Sheep saw service in various capacities, including Medical Unit Commander, in posts at Fort Myer, Va.; Fort Ethan Allen, Vt.; the Presidio, San Francisco, Calif.; Fort McKinley, Philippine Islands; Llano Grande, Tex.; Camp Greene, N. C.; Hoboken, N. J.; and New York City. In 1920 he was called to Washington for a tour of duty as Assistant Medical Officer in the Office of the Chief Surgeon of the Air Service.

The long-standing interest and special training of General Sheep in neuropsychiatry led in 1921 to his assignment as Chief of the Neuropsychiatric Section at Walter Reed General Hospital, where he remained until 1924. Following an eight-month course at the Mayo Foundation, Rochester, Minn., he was assigned (1925–26) to Letterman General Hospital, San Francisco.

Following his assignment at Letterman General Hospital, General Sheep held the posts of Executive Officer, Walter Reed General Hospital, Army Medical Center, Washington (1927–31); Acting Superintendent, Gorgas General Hospital, Ancon, Canal Zone (1932–34); Chief, Medical Service, Acting Commanding Officer and Executive Officer, Army and Navy General Hospital, Hot Springs, Ark. (1935–36); Chief, Military Personnel Division, Office of the Army Surgeon General, Washington (1937–40) and Post Surgeon, Fort McPherson, Ga. (1940–41).

It was from Fort McPherson that he was appointed to the command of Lawson General Hospital, Atlanta, Ga., a post which he held from 1941 until his retirement

in 1945. For his exceptionally meritorious conduct in the performance of outstanding services during these years, General Sheep was awarded the Legion of Merit by the War Department. He was promoted to Brigadier General in October, 1940. It is interesting to note that as early as 1920 he wrote an article on "The Flight Surgeon, a New Specialist in Medicine," which was published in the *Journal of the American Medical Association*.

General Sheep was a member of Delta Kappa Epsilon and Phi Chi fraternities. He was a member of the American Medical Association and a Diplomate of the American Board of Internal Medicine; he had been a Fellow of the American College of Physicians since 1928.

He is survived by his wife, Zaida Gannaway Sheep of Washington, and a daughter Carroll, who with her husband, Colonel John Voegtly, (MC), USA, is now living in Germany.

General Sheep was buried in Arlington National Cemetery on December 9 following funeral services in Walter Reed Memorial Chapel.

L. G. ALEXANDER, Lt. Col., MSC,
Chief Technical Liaison Office

DR. LOUIS F. WETTERBERG

Dr. Louis Ferdinand Wetterberg, F.A.C.P., who died December 10, 1952, was born in Perth Amboy, N. J., May 29, 1896. He attended Rutgers University, where he majored in Biological Sciences and Chemistry. Upon completion of his studies, he entered Harvard Medical School, where he received his medical degree in 1923.

Dr. Wetterberg served his internship at the Norwegian Lutheran Deaconesses' Home and Hospital, Brooklyn, N. Y., and did postgraduate work at Kings County Hospital, Brooklyn, as Resident in Neuropathology and also in Clinical Neurology. He was Assistant Neurologist in Kings County Hospital, Neurologist in Polhemus Memorial Clinic, Long Island College Hospital in Brooklyn, and also served in the Cardiac Clinic at Polhemus Memorial Clinic. He was Visiting Physician at the Cardiac Clinic, Newark Beth Israel Hospital, and was Attending Physician at the Perth Amboy General Hospital. Dr. Wetterberg was formerly Instructor in Neuropathology at the Long Island College of Medicine.

In 1928, Dr. Wetterberg traveled abroad, and while in Europe visited numerous university clinics, with a view toward broadening his training in Internal Medicine and Neurology.

He was a member of the Middlesex County Medical Society, the Medical Society of New Jersey and the American Medical Association. He had been a Fellow of the American College of Physicians since 1932.

In addition to his medical interests, Dr. Wetterberg was Vice President of the New Jersey Wood Finishing Company.

His death was a great loss to the community.

EDWARD I. MARGARETTEN, M.D. (Associate)

Fig. 1: "Roentgen examination . . . revealed the ulcer to be very much in evidence."

Fig. 2: In ten weeks "the ulcer niche was no longer in evidence roentgenologically or gastroscopically."

Clinical Evaluation of Pro-Banthine*

CASE REPORT

"M. D., female, aged 48, had a posterior gastrojejunostomy 14 years ago for duodenal ulcer. The patient was fairly well until nine months ago when severe, intractable pains occurred. She was hospitalized and a subtotal gastrectomy was done.

"She remained well for only a few months and was referred to us because of recurrence of very severe pain and marked weight loss. Roentgen study revealed a fairly large ulcer niche on the gastric side of the anastomosis.

"The patient had been on various types of antacids and sedatives without relief from pain. She was given 60 mg. of Pro-Banthine q.i.d. and within 72 hours was able to sleep through the night for the first time in weeks.

"At the end of two weeks of such treatment the patient had absolutely no pain and felt that she had been 'cured.' Roentgen examination at this time revealed the ulcer to be very much in evidence (*Fig. 1*). Much persuasion was necessary to make the patient realize the importance of maintaining her diet and therapy.

"Ten weeks of controlled regulation was necessary before we were satisfied that the ulcer niche was no longer in evidence roentgenologically or gastroscopically (*Fig. 2*).

"She has been maintained on 30 mg. [q.i.d.] of Pro-Banthine for almost five months with no recurrence of symptoms."

Schwartz, I. R.; Lehman, E.; Ostrov, R., and Seibel, J. M.: A Clinical Evaluation of a New Anticholinergic Drug, Pro-Banthine, to be published.

Pro-Banthine (*brand of propantheline bromide*), the new, improved anticholinergic agent, is more potent and, consequently, a smaller dosage is required and side effects are greatly reduced or absent.

Peptic ulcer, gastritis, intestinal hypermotility, pancreatitis, genitourinary spasm and hyperhidrosis respond effectively to Pro-Banthine, orally, combined with dietary regulation and mental relaxation.

*Trademark of G. D. Searle & Co.

SEARLE *Research in the Service of Medicine*

CLINICAL STAFF
PENNSYLVANIA

•

MEDICAL STAFF

Robert Devereux, M.D.
Ruth E. Duffy, M.D.
Herbert H. Herskovits, M.D.
Robert L. Hunt, M.D.
Joseph J. Peters, M.D.
Calvin F. Settlage, M.D.
A. Stephan Terzian, M.D.

•

PSYCHOLOGICAL STAFF

Edgar A. Doll, Ph.D.
Director of Research
Milton Brutten, Ph.D.
Michael B. Dunn, A.M.
Robert G. Ferguson, A.M.
Edward L. French, Ph.D.
Marguerite B. Horn, A.M.
John R. Kleiser, Ph.D.
Kathryn Kramer
Mary J. Pawling, A.M.
Jack Shelley, M.Ed.

maximum achievement and adjustment for the exceptional child . . .

TO the child whose learning is retarded by reason of organic involvement, Devereux Schools offer an educational and therapeutic program geared specifically to his needs. Methods and curriculum are evolved under the guidance of psychiatrists to create a program that will help the retarded child to develop psychically and academically to his fullest potential. Devereux' physical facilities offer careful grouping by mental, physical, and emotional level. Such grouping is of great therapeutic value.

You may have occasion to advise parents whose child is in need of this highly specialized attention. The Devereux Schools staff will be pleased to study the case carefully and offer a detailed report on the possibility of utilizing the Devereux program of education with therapy.

Please address your inquiries to: John M. Barclay, Registrar

DEVEREUX SCHOOLS

HELENA T. DEVEREUX, *Director* • J. CLIFFORD SCOTT, M.D., *Executive Director*

SANTA BARBARA, CALIFORNIA **DEVON, PENNSYLVANIA**

Binding your Annals?

Before you do, have you thought about the Jesse Jones Volume File? It holds an entire volume; each of the six issues is readily accessible.

- **ATTRACTIVE**—Red and green Kivar cover looks and feels like leather, and the hot-embossed 16-carat gold-leaf lettering makes it a fit companion for your finest bindings.
- **STURDY**—Will support 150 pounds; no danger of its being crushed by heavy books.
- **EXCLUSIVE**—Especially designed and produced for the *Annals of Internal Medicine*, and is available only from the College.
- **ECONOMICAL**—Sent postpaid, carefully packed, for $2.50 each, 3 for $7.00, or 6 for $13.00.

Please send me, postpaid,
.....VOLUME FILES, @ $2.50 each,
3 for $7.00 or 6 for $13.00.

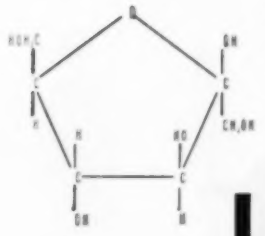
Name:.....

Address:.....

City:.....

Clip this coupon today for prompt shipment, and order direct from:

AMERICAN COLLEGE OF PHYSICIANS
4200 PINE ST., PHILADELPHIA 4, PA.



Levugen

(FRUCTOSE, MEAD)

the first solution of pure fructose for intravenous infusion

The advantages of fructose for intravenous infusion have long been recognized. But limited availability of pure fructose has prevented its general clinical use. Now, extensive research in carbohydrate chemistry by Mead Johnson & Company has resulted in a practical and economical method of producing pure fructose. As Levugen 10% in Water, it is available for intravenous use.

Levugen (Fructose, Mead) can be infused much more rapidly than dextrose, with better retention and less disturbance of fluid balance.

Since Levugen is removed from the blood very rapidly, it does not produce high hyperglycemic levels or spill over into the urine in significant amounts even when it is infused in fairly high concentration. Levugen can therefore be given much more rapidly than dextrose, with less loss of calories through glycosuria. A liter of Levugen 10% in Water can be given in the same time as a liter of 5% dextrose.

Clinical Advantages of Levugen

- More rapid provision of calories
- Less loss of calories through glycosuria
- More rapid formation of liver glycogen
- Less disturbance of fluid balance
- Shorter infusion time, with less discomfort for the patient
- Less time and trouble for hospital personnel

"Levugen" *can be infused more rapidly"*

Levugen 10% in Water is available in 1 liter (1000 cc.) flasks, containing 100 Gm. of Levugen (Fructose, Mead), approximately 400 calories.

Levugen
(FRUCTOSE, MEAD)

MEAD

MEAD JOHNSON & COMPANY
Evansville 21, Ind., U. S. A.

Aminodrox

Aminodrox

Aminodrox

Aminodrox

Aminodrox

Aminodrox

Heard at the staff meeting . . .

increases the usefulness of oral aminophylline

send for detailed literature and sample

THE S. E. MASSENGILL CO.

BRISTOL, TENNESSEE

In the form of AMINODROX, three out of four patients can be given therapeutically effective *oral* doses of aminophylline.

This is possible with AMINODROX because gastric disturbance is avoided.

How congestive heart failure, bronchial and cardiac asthma, status asthmaticus and paroxysmal dyspnea can be treated successfully with *oral* aminophylline in the form of AMINODROX.

Aminodrox Tablets contain 1 1/2 gr. aminophylline with 2 gr. activated aluminum hydroxide.

Aminodrox-Forte Tablets contain 3 gr. aminophylline with 4 gr. activated aluminum hydroxide.

Also available with 1/4 gr. phenobarbital.

diarrhea

has no seasonal bounds

STREPTOMAGMA produces prompt and complete remission in bacterial diarrheas. This modern anti-diarrhetic combines *Dihydrostreptomycin*, for its potent bacteriostatic action, particularly against diarrhea-causing coliform organisms; *Pectin*, for its demulcent and hydrophilic effect; *Kaolin*, for tremendous adsorptive power; and *Alumina Gel* . . . itself a potent adsorptive . . . soothing, protective suspending agent.

Supplied: Bottles of 3 fluidounces.
For a clinical sample, just write to Wyeth, Philadelphia 2, Pa.

Streptomagma*

DIHYDROSTREPTOMYCIN SULFATE AND PECTIN
WITH KAOLIN IN ALUMINA GEL

Wyeth®
Philadelphia 2, Pa.

*Trademark

Prelude to asthma?

not necessarily . . .

Tedral, taken at first sign of attack, often forestalls severe symptoms.

in 15 minutes...Tedral brings symptomatic relief with a definite increase in vital capacity. Breathing becomes easier as Tedral relaxes smooth muscle, reduces tissue edema, provides mild sedation.

for 4 full hours... Tedral maintains more normal respiration for a sustained period—not just a momentary pause in the attack.

Prompt and prolonged relief with Tedral can be initiated any time, day or night, whenever needed, without fear of incapacitating side effects.

Tedral provides:

theophylline	2 gr.
ephedrine	⅜ gr.
phenobarbital	⅛ gr.

in boxes of 24, 120 and 1000 tablets

Tedral

WARNER-CHILCOTT
Laboratories NEW YORK

"Bemotinic" Liquid

in the common anemias

Unequalled for taste
Unusually palatable. No need to dilute or mask . . . just a pleasantly rich orange flavor, with no aftertaste.

Effective action
Provides essential factors for maximal hemopoietic and clinical response . . . includes a B_{12} potentiator.

Simple administration
Directly from the spoon because of high degree of palatability . . . smooth, nonviscous, easy-pouring.

Palatable Orange Flavor Nonalcoholic

Each teaspoonful (5 cc.) contains:

Ferric ammonium citrate	200.0 mg.
Vitamin B_{12} U.S.P. (crystalline)	4.0 mcg.
Extractive as obtained from of fresh gastric tissue	450.0 mg.
Folic acid	0.33 mg.
Thiamine HCl (B_1)	1.5 mg.
Riboflavin (B_2)	1.0 mg.
Pyridoxine HCl (B_6)	0.2 mg.

Suggested dosage:
Adults: 1 to 2 teaspoonfuls
Children: ½ to 1 teaspoonful
Three times daily, or more as required.
No. 940 — Supplied in bottles of 16 fluidounces and 1 gallon.

Also available

"BEMOTINIC" CAPSULES

No. 340 — Bottles of 100 and 1,000.

Each capsule contains:

Ferrous sulfate exsic. (3 gr.)	200.0 mg.
Vitamin B_{12} U.S.P. (crystalline)	10.0 mcg.
Gastric mucosa (dried)	100.0 mg.
Desiccated liver substance, N.F.	100.0 mg.
Folic acid	0.67 mg.
Thiamine HCl (B_1)	10.0 mg.
Vitamin C (ascorbic acid)	50.0 mg.

Suggested dosage: 1 or 2 capsules three times daily, or as directed by the physician. Preferably taken with food.

5302-A

Ayerst, McKenna & Harrison Limited, New York, N. Y. • Montreal, Canada

Flavorsome Variety for

LOW SALT DIETS

For many salads and hot dishes.

CELLU BONED CHICKEN — Unsalted, boned, ready for use. Only 38 mg. sodium in 100 grams. In 5½ oz. cans.

CELLU BAKING POWDER—Sodium-Free. Use in same proportions as ordinary baking powder. In 4 oz. jars.

CELLU K-SALT — Sodium-Free. A salty tang to foods without adding sodium. 1¼ oz. shakers and 1 lb. containers.

Many Other Flavorsome Foods. Send for Free Catalog.

CELLU LOW SODIUM *Dietary Foods*

CHICAGO DIETETIC SUPPLY HOUSE *Inc.*
1750 West Van Buren Street Chicago 12, Illinois

THE
MEDICAL
PROTECTIVE
COMPANY
FORT WAYNE
INDIANA

PROFESSIONAL PROTECTION
EXCLUSIVELY
SINCE 1899

specialized service
assures *"know-how"*

Symbols of Fellowship

Every Fellow of The American College of Physicians prizes his Fellowship and should make use of these symbols to remind him, his associates and his patients of the ideals, aims and accomplishments of the College.

FELLOWSHIP KEY

This beautifully designed charm, bearing the seal of the College, is 10K solid gold and embossed in the College colors. Shown actual size. Initials of Fellow and date of election engraved on back at no extra charge. *Price, including tax, delivered, $7.50.*

FELLOWSHIP PLEDGE

All Fellows subscribe to this pledge at time of induction. Engraved with artist's outlined initials and the College seal in color; mounted and framed, with line for Fellow's signature. Ideal for reception room or office. *Price, framed and delivered, $7.50.*

FELLOWSHIP CERTIFICATE FRAME

The Fellowship Certificate furnished without charge to newly elected Fellows should be protected and displayed in the official, distinctive frame. Similar in design to Pledge frame; attractively finished in gold. Shipped without glass. *Price, delivered, $4.50.*

AS A GIFT

To a Fellow, for that birthday or anniversary, or for any occasion, the Fellowship Key, Fellowship Pledge or Certificate Frame is ideal. These symbols of Fellowship become treasured possessions; reminders of high purpose and achievement.

Order now from:

The American College of Physicians
4200 Pine Street, Philadelphia 4, Pa.

Tryptar Debridement in Crush Injury of Buttock

Tryptar is also effective in the everyday management of varicose ulcers, in burns, soft tissue abscesses, osteomyelitis, fistulae and sinus tracts.

to effect Physiologic Debridement

WITHIN HOURS

Tryptar dissolves necrotic tissue, surface coagula, clotted blood, purulent secretions and fibrinous strands by physiologic enzymatic action. So rapid is debridement on external lesions that excellent clearing may be obtained within hours. Tryptar acts with complete safety because it cannot digest viable cells or connective tissue. Neither sensitivity to Tryptar nor antigenicity have been reported.

Also available as Tryptar Aerosol for introduction into the respiratory tract. Clogging purulent bronchial secretions are rapidly liquefied and can be easily expectorated.

For detailed information write Medical Service Dept., The Armour Laboratories, 520 N. Michigan Avenue, Chicago 11, Illinois.

Tryptar

The Armour Laboratories Brand of Purified Crystalline Trypsin

THE ARMOUR LABORATORIES

A DIVISION OF ARMOUR AND COMPANY • CHICAGO 11, ILLINOIS

-world-wide dependability-

PHYSIOLOGIC THERAPEUTICS THROUGH BIORESEARCH

DOCK* BALLISTOGRAPH

**As described by William Dock, M.D., et al. Vol. 146, No. 14, Aug. 4, 1951, Jl. A. M. A. Ballistocardiography in Med. Prac.*

Compact design, engineered for accuracy, simplicity of use and clinical efficiency. No service required. Records on any make ECG. Simultaneous QRS reading.

$50.00 F.O.B. NEW YORK

With "leg block" carrying case— $12.50 extra

COUNTY SURGICAL CO., INC.

1237 Atlantic Ave., Brooklyn 16, N. Y.

WANTED

Back Issues of ANNALS OF INTERNAL MEDICINE

Good used copies of the *following* issues are now needed. Only those issues which are currently being advertised can be accepted.

$1.00 each for

Vol.	I, No. 1—July, 1927
Vol.	I, No. 2—August, 1927
Vol.	I, No. 3—September, 1927
Vol.	I, No. 4—October, 1927
Vol.	I, No. 5—November, 1927
Vol.	I, No. 6—December, 1927
Vol.	I, No. 7—January, 1928
Vol.	I, No. 8—February, 1928
Vol.	I, No. 9—March, 1928
Vol.	I, No. 10—April, 1928
Vol.	II, No. 1—July, 1928
Vol.	II, No. 4—October, 1928
Vol.	II, No. 5—November, 1928
Vol.	IV, No. 10—April, 1931
Vol.	VI, No. 1—July, 1932
Vol.	VI, No. 4—October, 1932
Vol.	VI, No. 8—February, 1933
Vol.	VII, No. 1—July, 1933
Vol.	VII, No. 2—August, 1933
Vol.	XXXVI, No. 1—January, 1952

75¢ each for

Vol. XXXVIII, No. 1—January, 1953	
Vol. XXXVIII, No. 2—February, 1953	

Address Journals to:

E. R. LOVELAND, Executive Secretary
4200 Pine Street Philadelphia 4, Pa.

INDEX TO ADVERTISERS

May, 1953

Abbott Laboratories 16–17, 44
Ames Company, Inc. 4
Appleton-Century-Crofts, Inc. .. Second Cover
Armour Laboratories, The 28, 31, 59
Ayerst, McKenna & Harrison Limited 12, 36, 57
Brewer & Company, Inc. 38
Briggs Company, The 2
Burroughs Wellcome & Co. (U. S. A.) Inc. 18
Burton, Parsons & Co. 37
Chicago Dietetic Supply House, Inc. 58
Ciba Pharmaceutical Products, Inc. ... 19, 32
County Surgical Co. 60
Davies, Rose & Company, Limited 45
Devereux Schools 52
Dietene Company, The 39
Endo Products, Inc. 48–49
Flotill Products, Incorporated 10
E. Fougera & Company, Inc. 34
Foundation Laboratories, Inc. 25
Geigy Pharmaceuticals 30
General Electric Company, X-Ray Dept .. 13
Paul B. Hoeber, Inc. 3
Hoffmann-La Roche, Inc. insert facing page 24
Irwin, Neisler & Co. 6, 22
Thos. Leeming & Co., Inc. 14
Eli Lilly and Company 5
Lloyd Brothers, Inc. 8–9
Macmillan Company, The 1
S. E. Massengill Company, The 43, 54
Mead Johnson & Company 46, 53
Medical Protective Company, The 58
Merck & Co., Inc. 29
Wm. S. Merrell Co., The insert facing page 32
Oxford University Press, Inc. 2
Parke, Davis & Company 23
E. L. Patch Company 24
Chas. Pfizer & Co., Inc. ..... 41, Third Cover
William H. Rorer, Inc. 27
Sanborn Co. 40
Schenley Laboratories, Inc. 47
Schering Corporation 15
G. D. Searle & Co. 51
Sharp & Dohme 50
Smith, Kline & French Laboratories ... 21, 61
E. R. Squibb & Sons 42
U. M. A. Inc. 62
Upjohn Company, The 35
Varick Pharmacal Co., Inc. 33
Wander Company, The 20
Warner-Chilcott Laboratories, Inc. 7, 56
Winthrop-Stearns Inc. 26
Woodward Medical Personnel Bureau 6
Wyeth Incorporated 11, 55

in the treatment of sick old people...

... to establish a more cooperative attitude in the "difficult" patient ... to relieve anxiety and irritability ... to overcome "confusion" and depression ... to revive interest in life and living ... to encourage activity and a sense of usefulness, prescribe ...

DEXAMYL* tablets and elixir

Each 'Dexamyl' tablet (or one teaspoonful of elixir) contains Dexedrine* Sulfate (dextro-amphetamine sulfate, S.K.F.), 5 mg., and amobarbital (Lilly), ½ gr.

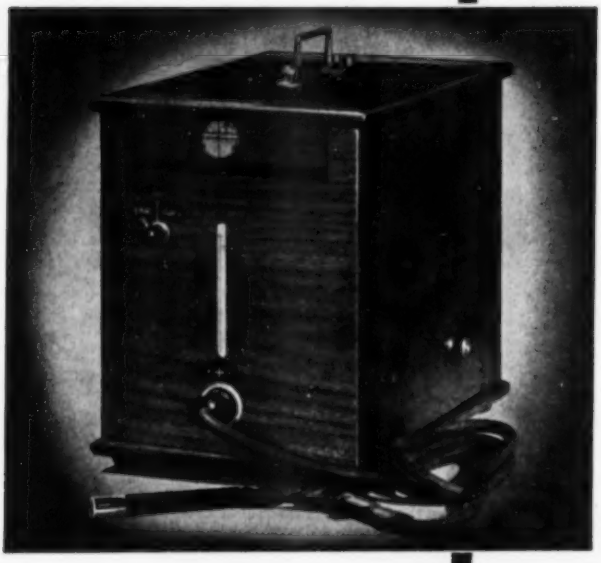
Smith, Kline & French Laboratories, Philadelphia

*T.M. Reg. U.S. Pat. Off.

THE U.M.A. THERMOCOUPLE

is extremely important for determining the presence of Peripheral Vascular Disease.

For taking skin and subsurface temperatures instantaneously and accurately the U. M. A. THERMOCOUPLE is the standard the world over



Any number of consecutive direct readings can be rapidly taken without lag or calculations of any kind.

Accurate, soundly engineered and sturdily built to give a long period of carefree service. No batteries.

Indicates instantly in Fahrenheit and Centigrade.

The U. M. A. THERMOCOUPLE is extremely low in price **$125.00**

At your Dealer or send for literature.

The COLLENS SPHYGMO-OSCILLOMETER

(not illustrated)

is the most important diagnostic aid in Peripheral Vascular Diseases. A blood pressure apparatus and an oscillometer in one instrument **$42.00**

The COLLWIL INTERMITTENT VENOUS OCCLUSION APPARATUS

(not illustrated)

is the proved and accepted single and automatic therapy whenever impairment of arterial circulation of the limbs occurs. **$177.00**

U.M.A. Inc.

56 Cooper Square, New York 3, N. Y.

Algonquin 4-0924

antibacterial activity of penicillin and dihydrostreptomycin synergistically combined for greater therapeutic efficacy and convenience in

Combiotic®

providing both antibiotic agents for treatment of certain mixed bacterial infections, particularly urinary tract infections, penicillin-resistant gonococcal infections, complications of upper respiratory infections and other infections caused by susceptible organisms.

Pfizer world's largest producer of antibiotics

Supplied as

Combiotic Aqueous Suspension *in 5-dose (10 cc.) drug-clear vials containing 400,000 units penicillin G procaine crystalline and 0.5 Gm. dihydrostreptomycin sulfate in each dose*

Steraject® *Combiotic Aqueous Suspension single-dose disposable cartridge*

Combiotic P-S (dry powder) ***1.0 Gram Formula*** *containing in each dose 300,000 units penicillin G procaine crystalline, 100,000 units buffered penicillin G sodium crystalline plus 1.0 Gm. dihydrostreptomycin sulfate*

Combiotic P-S (dry powder) ***New 0.5 Gram Formula*** *containing 300,000 units penicillin G procaine crystalline, 100,000 units buffered penicillin G sodium crystalline plus 0.5 Gm. dihydrostreptomycin sulfate*

®Trademark, Chas. Pfizer & Co., Inc.

Antibiotic Division
Chas. Pfizer & Co., Inc.
Brooklyn 6, N. Y.

ANNALS OF INTERNAL MEDICINE

OFFICIAL PERIODICAL OF THE AMERICAN COLLEGE OF PHYSICIANS

EDITOR

MAURICE C. PINCOFFS, M.D., Baltimore

ASSISTANT EDITOR

PAUL W. CLOUGH, M.D., Baltimore

ASSOCIATE EDITORS

DAVID P. BARR, M.D., New York
JAMES H. MEANS, M.D., Boston
ROBERT A. COOKE, M.D., New York
O. H. PERRY PEPPER, M.D., Phila.
JAMES J. WARING, M.D., Denver

EXECUTIVE SECRETARY

EDWARD R. LOVELAND, Philadelphia

Editorial Office—University Hospital, Baltimore 1, Maryland
Executive Office—4200 Pine Street, Philadelphia 4, Pa.
Place of Publication—Prince & Lemon Sts., Lancaster, Pa.

MANUSCRIPTS. All correspondence relating to the publication of papers and all books and monographs for review should be addressed to the Editor. Bibliographic references are to conform to the following style:

4. Doe, J. E.: What I know about it, J. A. M. A. 96: 2006, 1931.

Six illustrations per article are allowed without cost to the author. Beyond this number the author must pay the actual cost of illustrations.

REPRINTS. For each article published, there will be furnished gratis fifty reprints without covers. An order slip for additional reprints, with a table showing cost, will be sent with galley proof to each contributor. If additional reprints over the first fifty are wanted the order slip must be returned to the printer at the time corrected galley proofs are sent to the Editor.

REVIEWS. Selected monographs and books in the field of internal medicine will be reviewed monthly in the ANNALS. Authors and publishers wishing to submit such material should send it to the Editor. Since it is not possible to review all books submitted, a monthly list of all those received will be published in the review section.

SUBSCRIPTION. This periodical is issued monthly, new volumes beginning with the January and July numbers of each year. Subscription price per annum, net postpaid: $10.00, United States, Canada, Mexico, Cuba, Canal Zone, Hawaii, Puerto Rico, Philippine Islands, Central and South American Countries, and Spain; $7.00, in the above countries, to bona fide medical students, interns and residents; $11.00, other countries. Prices for back numbers furnished upon application. Single numbers, current volume, when available, $1.25. Checks should be drawn to the order of W. D. STROUD, M.D., Treasurer, and remitted through the Executive Secretary's Office.

BUSINESS CORRESPONDENCE. All correspondence relating to business matters, advertising, subscriptions to the ANNALS, inquiries concerning membership in the American College of Physicians, et cetera, should be addressed to the Executive Secretary. Books and reprints presented to the College Library should be addressed to the Executive Secretary.

LANCASTER PRESS, INC., LANCASTER, PA.